Chapter 4

Perioperative Care and Management of Complications in Pancreatic Surgery

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Abstract

Pancreatic surgeries, including pancreaticoduodenectomy, are complex surgical procedures. There is increasing interest in implementing comprehensive perioperative protocols to improve the success of surgery. Patients are often elderly and may have significant comorbidities and malnutrition. Careful patient selection, appropriate preoperative evaluation and optimization can greatly contribute to a favorable outcome after major pancreatic resections. In recent years, along with advances in anesthesia and intensive care practice, the mortality rates have reduced significantly. On the other hand, the morbidity rates are still as high. Therefore it is important to understand that a multidisciplinary professional system is crucial to reduce mortality and morbidity in pancreatic surgery.

Introduction

Pancreatic surgery is performed as a result of benign or malignant causes. Cystic pancreatic tumors, pancreatic complications, and trauma are among the benign reasons for pancreatic surgery.

Presently, the most common reason for pancreatic surgery is pancreatic cancer. Pancreatic cancer can be located in the head, body, or tail of the pancreas. The pancreatic head cancer is the most common location. For this reason, the most common surgical procedure in pancreatic cancer is the pancreaticoduodenectomy [1]. On the other hand, total pancreatectomy or distal pancreatectomy can be applied for tumors located in the body and tail.
of the pancreas. The pancreaticoduodenectomy is also the preferred surgery for other tumors in the periampullary regions.

Pancreatic cancer is the ninth most common cancer in the world and is the fourth leading cause of cancer-associated deaths. Every year, 138,100 men and 127,900 women are expected to die from pancreatic cancer. Furthermore, the life expectancy of patients diagnosed with pancreatic cancer is less than 5%. It is 1.3 times more common in males and its incidence increases with age [2,3]. The most important and the most effective treatment of pancreatic cancer is surgery. However, only 15-20% of diagnosed patients are eligible for surgery. After successful surgery, the average 5-year survival is 25-30% [4].

Pancreatic surgeries, including pancreaticoduodenectomy, are complex surgical procedures that might disrupt the function and integrity of the gastrointestinal tract. Pancreatic surgeries were always associated with high mortality and morbidity rates due to either technical difficulty during the operation or the effects of surgery on metabolism. However, in recent years, along with advances in anesthesia and intensive care practice, the mortality rates have reduced significantly. Some centers have reported that their pancreatic surgery associated mortality rates were 2-5%, while some high-volume centers reported rates lower than 2%. On the other hand, the morbidity rates are still as high as 30-65% [2]. Therefore, a multidisciplinary approach is needed for implementation of a surgical procedure with such a high morbidity rate. Lower mortality and morbidity rates have been reported when the pancreatic surgery is performed in high-volume centers [1]. Lieberman et al. evaluated a total of 1971 pancreatectomy procedures conducted in 184 centers, including a center in New York. According to this study, the mortality rate was 4% in centers that performed more than 40 pancreatectomy procedures per year, while it was 12.3% in centers that performed less than 40 [1]. Several other studies have also reported lower mortality, length of hospital stay, and cost in high volume centers [13-15]. The most important reason for that is that the management of perioperative care and postoperative complications are standardized in such centers.

**Preoperative Evaluation, Preparation and Risk Scores**

Following the diagnosis of pancreatic cancer, patients should be evaluated in terms of conformity for surgery, which begins by determining the extent of the tumor. Patients are divided into three groups: patients that are not candidates for surgery due to disseminated disease, patients with locally advanced disease, and patients that are eligible for surgery. The patients that eligible for surgery are further evaluated in terms of absence of celiac trunk, superior mesenteric artery and hepatic artery involvement, and no evidence of superior mesenteric vein and portal vein invasion [5]. Patients that have a borderline
resectable tumor can be directed to the neoadjuvant treatment. However, patients that have borderline resectable tumors, also have long segment, and don’t have more than 180-degree artery involvement can also be recommended for surgery [6-9].

After evaluating patients’ technical eligibility for surgery, it is important to assess the surgical risk. Pancreatic cancer peaks in the seventh and eighth decades, therefore most of the patients undergoing surgery are geriatric patients. The physiological changes and comorbidities accompanying old age may not allow for complex abdominal surgery. Many studies have indicated that old age alone is not contraindication for surgery. However, it is important to correctly evaluate specific changes and comorbidities related to this patient group and provide optimal surgical conditions as well as post-operative care [10-12].

Correct and adequate assessment of patients in the preoperative stage allows for comfortable and easy intraoperative and postoperative care. Specific evaluations pertaining to individual characteristics of each patient must be done in order to achieve the aforementioned kind of care. Moreover, the combination of many factors should be considered when assessing the risk of surgical intervention. Patient related risks are comorbid diseases, the duration of disease, and the ability to tolerate the physiological stress due to surgical procedure.

Several scoring systems have been created to evaluate possible surgery and anesthesia related mortality and morbidity risks. These systems are generally based on the data obtained from patients during pre-hospitalization and hospitalization periods. Moreover, they can provide a relationship between the patient data and the extent of the surgical procedure. Along with physiological scoring systems that determine the risk based on the preoperative state of organ systems, there are preoperative systems that assess the overall preoperative health state of patients [16,18,21]. In order to evaluate patients using these systems, detailed assessment of cardiological, respiratory, neurological, gastrointestinal, and nephrological systems should be performed. These scoring systems are summarized in Table 1.

**Table 1: Perioperative scoring systems.**

<table>
<thead>
<tr>
<th>Physiological scoring systems</th>
<th>Preoperative scoring systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE(I,II)</td>
<td>ASA</td>
</tr>
<tr>
<td>E-PASS</td>
<td>Goldman cardiac risk index</td>
</tr>
<tr>
<td>ISS/TRISS</td>
<td>Hospital prognostic index</td>
</tr>
<tr>
<td>POSSUM</td>
<td>Prognostic nutritional index</td>
</tr>
<tr>
<td>P-POSSUM</td>
<td>Risk of pulmonary complications</td>
</tr>
<tr>
<td>SAPS</td>
<td></td>
</tr>
<tr>
<td>Sepsis score</td>
<td></td>
</tr>
<tr>
<td>Disease score</td>
<td></td>
</tr>
<tr>
<td>Treatment-related intervention score</td>
<td></td>
</tr>
</tbody>
</table>
Goldman Cardiac Risk Index [22] is probably one of the best models that evaluate cardiac risk with regards to surgery. Scoring is done by nine different clinical factors and patients are divided into four risk groups based on their total score (Table 2).

**Table 2: Goldman cardiac risk index.**

<table>
<thead>
<tr>
<th>Causes of cardiac risk</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction within the last 6 months</td>
<td>10</td>
</tr>
<tr>
<td>Age&gt;70</td>
<td>5</td>
</tr>
<tr>
<td>Severe stenosis of aortic valve</td>
<td>11</td>
</tr>
<tr>
<td>Non-sinus rhythm in the preoperative ECG or atrial premature beats with sinus rhythm</td>
<td>3</td>
</tr>
<tr>
<td>More than five premature ventricular contractions per minute in the preoperative period</td>
<td>7</td>
</tr>
<tr>
<td>Worsening of general condition</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal, thoracic or aortic surgery</td>
<td>3</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>4</td>
</tr>
</tbody>
</table>

The American Society of Anesthesiologists (ASA) scoring system (Table 3) was initially developed to inform the anesthetist about patients’ comorbid diseases. Due to its ease of use and lack of need for additional testing, ASA continues to be used in order to assess surgery related risks. The ASA scoring system is directly associated with perioperative variables, such as perioperative morbidity and mortality, as well as blood loss during surgery, postoperative ventilation time, and length of stay in intensive care. It has been shown that postoperative morbidity increases proportionally with the size of surgical intervention, ASA class, respiratory disease symptoms, and the presence of tumor [17].

**Table 3: ASA Classification.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Point</th>
<th>Risk of life-threatening complications</th>
<th>Risk of cardiac death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0-5</td>
<td>0,7</td>
<td>0,2</td>
</tr>
<tr>
<td>II</td>
<td>6-12</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>3-25</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>≥26</td>
<td>22</td>
<td>56</td>
</tr>
</tbody>
</table>

Nutritional assessment is important in terms of evaluating patients’ physiological state, immunological function, and fluid balance as well as regulating patients’ metabolic responses to trauma and surgery. Loss of 10% of body weight in the last 6 months and albumin values lower than 3g/dL allow for patients to be diagnosed with malnutrition. The frequency of postoperative complications in patients with malnutrition is higher, therefore these patients should be provided with nutritional support for at least 2 weeks prior to surgery [23]. The prognostic nutritional index (PNI) has been developed for the prediction of mortality-related risk of complications and is directly proportional with postoperative sepsis and death.
The following four factors are used in PNI: serum albumin levels, serum transferrin levels, delayed skin hypersensitivity, and triceps muscle skinfold thickness. The first three of these factors are definitively associated with postoperative morbidity and mortality. Furthermore, PNI can also be used for the prediction of the need for nutrition support in the perioperative period.

Acute Physiology and Chronic Health Evaluation (APACHE) scoring system was first defined in 1981 and amended in 1985 as APACHE II system. Although this scoring system was first developed for patients in the intensive care unit, later it has been used for the evaluation of clinical conditions in severe trauma, abdominal sepsis, postoperative enterocutaneous fistula, and acute pancreatitis along with the prediction of postoperative outcome. The disadvantages of APACHE II system are its relative complexity and failure to consider cardiac symptoms that can increase the patient’s nutritional status and surgical risk. In addition, the size of the surgical intervention is not considered to be a factor in the APACHE II system. Recently, APACHE III system has also been developed but is considered to be too complicated for routine use [19].

The Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) was developed with the aim of grading predicted mortality and morbidity. The POSSUM provides multivariate disintegration analysis of retrospective and prospective data in order to evaluate the quality of surgical follow-up care. The POSSUM calculates predicted mortality and morbidity rates based on 6 surgical and 12 physiological variables that are scored as 1, 2, 4, or 8 (Table 4). The biggest advantage of this system is the ability to predict both the mortality and morbidity. Moreover, it allows for successful comparison of performance between surgery centers, hospitals, and countries. On the other hand, the disadvantage of the POSSUM scoring system is not taking into account factors that may affect the results of surgery, such as operating time and differences between surgeons and anesthetists. Therefore, other additional factors should also be considered when POSSUM is used in patients undergoing surgery. Another disadvantage is that primary diagnosis is not used as a factor in the POSSUM scoring system. Nevertheless, when POSSUM and APACHE II systems were compared, the POSSUM has been shown to be superior in terms of identifying mortality risks in patients in the intensive care unit following a general surgery. A problem with the POSSUM system is that it has a minimum mortality of 1.1% and is six times more likely to predict mortality and morbidity, which may lead to a greater number of false positives. In order to overcome these disadvantages, P-Portsmouth POSSUM (P-POSSUM) system was developed by using different mathematical formulas. P-POSSUM’s minimum mortality rate was reduced to 0.2%. Furthermore, Chen et al. compared P-POSSUM and POSSUM systems in terms of predicting the mortal-
ity and morbidity in hepatopancreatobiliary surgery. They concluded that these scores were insufficient in making a proper assessment and suggested that more studies with additional parameters are needed [25].

Table 4: Parameters used to calculate the POSSUM score.

<table>
<thead>
<tr>
<th>Physiological Parameters</th>
<th>Surgical Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>Size of the operation</td>
</tr>
<tr>
<td>Cardiac symptoms/Posteroanterior lung x-ray</td>
<td>Multiple procedures</td>
</tr>
<tr>
<td>Respiratory symptoms/Posteroanterior lung x-ray</td>
<td>Blood loss (ml)</td>
</tr>
<tr>
<td>Pulse</td>
<td>Peritoneal damage</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Glasgow coma score</td>
<td>Type of surgery</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>Leukocyte count (x10^9)</td>
<td></td>
</tr>
<tr>
<td>Urine (mmol/l)</td>
<td></td>
</tr>
<tr>
<td>Na⁺ and K⁺ levels (mmol/l)</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td></td>
</tr>
</tbody>
</table>

The most common complications following pancreatic surgery are delayed gastric emptying, pancreatic fistula, wound site infection, and cardiopulmonary incidents. The rate of these complications remains high even in high-volume centers; therefore various, different special scoring systems are being developed for predicting complications and planning appropriate treatment approaches. There are scoring systems that can evaluate preoperative evaluation findings, intraoperative, and postoperative findings either separately or by combining all of these parameters.

In 2007, Assifi Mura et al. evaluated the value of Surgical Apgar Score (SAS), which was recommended by Gavende et al. and is used in many surgical procedures to predict mortality and morbidity, in pancreatic surgery [26,27]. The postoperative complications were calculated by SAS based on intraoperative bleeding, mean blood pressure, and pulse rate values; furthermore, they were classified and compared based on the morbidity score proposed by Clavien et al [28]. The grade 1-2 of this classification comprises of complications that do not lead to any changes in normal postoperative course, and the ones that do not require either reoperation or endoscopic and radiological procedures. Wound site infections that can be treated at bedside also fall into this group. Grade 3 complications include complications that require surgical, endoscopic, or radiological intervention; while grade 4 includes complications that require intensive care and may lead to organ failure; lastly, grade 5 complications are the ones that result in death. In this study, low SAS scores were shown to be effective in predicting morbidity and the development of pancreatic fistula; however, it was not effective in predicting mortality.

The most common pancreatic surgery specific complication is pancreatico-digestive anastomosis, which includes bleeding due to the development of pancreatic fistula, bilioenteric anastomosis complications, and intra-abdominal collections. Soft pancreas, pancreatic duct that is not expanded, and extensive intraoperative bleeding
were identified as independent risk factors for development of pancreatic fistula [29]. Moreover, elevated serum amylase levels on day zero of the surgery have been shown to indicate the development of pancreatic fistula [30]. Palani Velu et al. investigated the effectiveness of serum amylase and C-reactive protein in predicting pancreas specific complications. They reported that serum amylase levels below 130 units/l on postoperative day zero and C-reactive protein levels below 180mg/l on postoperative day 2 were associated with low morbidity and that patients with these parameters were suitable for early discharge [31].

Callery et al. have worked on a clinical risk scoring system that predicts development of severe pancreatic fistula. Soft pancreas, pancreatic duct that is not expanded, pathologies other than pancreatic adenocarcinoma, and chronic pancreatitis as well as extensive intraoperative blood loss have been identified as risk factors and assigned scores. The scoring is done from 1 to 10 and the authors showed that their scoring was effective in predicting development of fistula [32].

During the preoperative preparation it is important to evaluate patients’ cardiovascular system, nutritional status, and scoring systems along with blood tests. Patients with anemia can tolerate the surgery well unless they have other diseases; therefore, there is no need for preoperative blood transfusion when excessive blood loss is not expected during the surgery. The importance of determining blood groups and doing cross-comparison is obvious for patients scheduled for major surgery, where significant blood loss may develop. Prior to major surgery, medical files of even the patients that are not expected to require transfusion or cross-comparison should contain information regarding their blood type. This way, a two-level security system is created, where an emergency blood transfusion can be performed speedily in the event of the development of intraoperative bleeding and the risk of transfusion reactions is eliminated. When extensive blood loss is not expected during the surgery, anemia rarely results in changes in treatment strategies. Allogenic transfusion can be applied to anemic patients undergoing elective surgery in the preoperative period [33].

Antibiotic prophylaxis prior to pancreatic surgery and continuation of postoperative antibiotic use is another controversial issue. Antibiotic prophylaxis is implemented in abdominal surgeries according to the infectious diseases guidelines and the Surgical Care Improvement Project (SCIP) recommendations. However, prophylaxis applied based on these protocols has been shown to be inadequate in preventing wound infections in pancreaticoduodenectomy [34]. The most important reasons for this are the biliary stents that are applied prior to the surgery and biliary bacterial contamination. Therefore, a bile culture should be taken from each patient during the surgery, which will help determine the patient’s antibiogram protocol. Proph-
ylaxis will be administered according to this protocol and based on the culture results, it will be determined whether or not to continue the antibiotic treatment and which antibiotic to use in the post-operative period [35,36].

According to the venous thromboembolism prophylaxis guideline criteria, pancreatic surgery falls into the middle-high group [37] (Table 5). However, in prophylaxis with low molecular weight, heparin is usually avoided due to the concern that it might increase postoperative bleeding complications. Hayashi et al. have investigated the effects of thromboembolism prophylaxis on bleeding complications [38]. They concluded that although prophylaxis increased the risk of minor bleeding complications, there was no significant increase in the risk of major complications. Moreover, the prophylaxis resulted in a decrease in thromboembolic complications. Based on these results, thromboembolism prophylaxis is beneficial in pancreatic surgery and can be safely administered. The duration of prophylaxis is another issue for discussion. In a Cochrane analysis performed by Rasmussen et al., it indicated that prolonged prophylaxis in major abdominal surgeries decreased thromboembolic complications. They therefore recommended this type of prophylaxis [39]. In addition, there are also studies in literature that report the benefits of prophylaxis throughout treatment in cancer patients receiving chemotherapy [40]. Another important issue is how to approach patients that use acetylsalicylic acid for reasons such as coronary artery disease, where discontinuation might pose a risk to patients. While the general approach has been to discontinue acetylsalicylic acid 7-10 days before surgery, more recently surgeries are performed while patients are still on acetylsalicylic acid in order to avoid the risk of cardiac failure. Andrea et al. have shown that there was no increase in postoperative complications in patients that underwent surgeries without discontinuation of acetylsalicylic acid. Currently, the recommended approach in pancreatic surgery is the use of acetylsalicylic acid throughout the perioperative period without any interruption [41].

One of the most controversial issues that impacts morbidity in pancreatic surgery is whether the bilayer drainage should be performed in patients with high preoperative bilirubin levels; and if it needs to be done, then what method of bilayer drainage should be chosen. The purpose of drainage is to reduce potential mortality and morbidity as well as to relieve patients’ rash symptoms and treat cholangitis. However, there are several studies indicating that hyperbilirubinemia may increase the risk of surgery-related mortality and morbidity. Sugiyama et al. have conducted an extensive review of literature on this subject [42]. Based on the results of many studies, they suggested that given the possibility that preoperative biliary drainage can increase the risk of postoperative complications, it should only be performed in selected cases that have severe cholangitis or malnutrition. When the surgery is scheduled in the early stages the drainage is
not recommended. On the other hand, many studies have reached a consensus about which method of drainage to use when necessary. Since percutaneous biliary drainage poses a risk of spreading the tumor, the method of choice is stenting with metal or plastic stents by using the endoscopic method.

**Table 5: Venous thromboembolism prophylaxis based on risk classification.**

<table>
<thead>
<tr>
<th>Risk type</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>Minor surgery, no additional risk factors</td>
<td>Major abdominal surgery Age&gt;40 No additional risk factor</td>
<td>Major abdominal surgery Age&gt;60 Additional risk factor</td>
<td>Major abdominal surgery History of major venous thromboembolism Hypercoagulopathy disorders</td>
</tr>
<tr>
<td>Deep vein thrombosis risk</td>
<td>2%</td>
<td>10-20%</td>
<td>20-40%</td>
<td>40-80%</td>
</tr>
<tr>
<td>Pulmonary emboli risk</td>
<td>0.2%</td>
<td>1-2%</td>
<td>2.4%</td>
<td>4-10%</td>
</tr>
<tr>
<td>Primary prophylaxis</td>
<td>No need IPC</td>
<td>LDUH(5000U 3 times a day) Or LMWH(Deltaparin 5000U/day or Enaxiparin 4000U/day or Tinzaparin 4500U/day)</td>
<td>LDUH(5000U 3 times a day) Or LMWH(Deltaparin 5000U/day or Enaxiparin 4000U/day or Tinzaparin 4500U/day)</td>
<td>IPC Or LDUH(5000U 2 times a day) Or LMWH(Deltaparin 2500U/day or Enaxiparin 2000U/day or Tinzaparin 3500U/day)</td>
</tr>
<tr>
<td>Alternative prophylaxis</td>
<td>No need IPC</td>
<td>IPC</td>
<td>Heparin and IPC</td>
<td></td>
</tr>
</tbody>
</table>

IPC: Intermittent Pneumatic Compression; LDUH: Low Dose Unfractioned Heparin; LMWH: Low Molecular Weight Heparin.

**Intraoperative Stage**

The importance of intraoperative period and early postoperative period in the evaluation of perioperative period has been raised in recent years.

There are several studies comparing differences in perioperative care at both low and high mortality hospitals. In these studies using intraoperative hemodynamic monitoring, perioperative sequential compression devices, postoperative venous thromboembolism chemoprophylaxis and epidural catheters for effective pain control are found the factors to be important for reducing mortality and morbidity rates. Epidural catheters provide superior pain control and reduce the incidence of cardiopulmonary complications, compared to systemic opioid [47-50].

Recently there are studies which evaluate the relationship between perioperative fluid resuscitation and postoperative complications in patients undergoing pancreaticoduodenectomy. It is well known that patients frequently receive large volumes of intravenous fluid during and following major intraabdominal operations with the intention of replacing operative fluid losses. However the impact of fluid resuscitation on the development of postoperative complications is examined. Liberal fluid administration is correlated with bowel edema and anastomotic compromise. It is well documented that increased perioperative fluid especially in the early postoperative period is associated with increased major adverse events. Finally
restrictive fluid protocols especially in patients at high risk of anastomotic compromise are recommended [43-46,51].

Enhanced Recovery after Surgery (ERAS) protocols are comprehensive multimodal perioperative care pathways designed to optimize patient outcomes after major surgery.

ERAS protocols are multidisciplinary, include preoperative, intraoperative, and postoperative elements, and are designed to optimize outcomes by reducing surgical stress and supporting organ function [52]. There are two essential and relatively novel components of ERAS. These fundamental components are; restriction of IV fluid administration and preoperative carbohydrate loading in order to avoid insulin resistance. However, the effectiveness and outcomes of ERAS protocols after pancreas surgery is controversial. In their study, Morgan et al. have shown that “Enhanced Recovery after Surgery” is safely applicable procedure. Furthermore, they have suggested that this procedure decreases postoperative morbidity, especially delayed gastric emptying [53]. Overall, this approach is valuable in terms of demonstrating all-important factor is the system, not the surgeon himself in major abdominal operations.

**Postoperative Period**

Postoperative care includes; close monitoring of patient’s vital signs and fluid balance, wound care, following-up of drains, evaluating possible risk factors and administering appropriate medications. This period starts immediately after the operation and continues until the 30th postoperative day.

Initially, controlling the patient’s pain is vital in order to improve quality of life and to reduce cardiac and respiratory complications [54]. During the early postoperative period, to prevent respiratory complications, early mobilization and standard respiratory physiotherapy are two key elements. Additionally, early mobilization accelerates the recovery time of gastrointestinal motility.

As it is defined in ERAS protocol; nasogastric tubes are avoided or removed early. In the same way, Foley catheters are also recommended to be removed early. In this protocol, prolonged postoperative fasting is avoided. Besides, early enteral nutrition is essential.

A moderate to severe risk of malnutrition was identified in 52-88% of patients who underwent pancreatic resection for cancer. This malnourished state, either it is evident or not, is associated with increased morbidity and mortality [55].

Therefore, nutrition plays an integral role in pancreatic cancer surgery, not only preoperatively, but also in the postoperative period. According to observational studies and available randomized control trials in pancreatic surgery, and additional literature from other surgical disciplines, oral feeding at will, recognized as the best approach. On the other hand, if preoperative nutritional
support was initiated due to insufficient nutrition it would be appropriate to continue after surgery according to current guidelines [56]. As generally recognized, parenteral nutrition is associated with an increased risk of complications. However, this is beneficial during postoperative period of undernourished patients, in whom enteral nutrition is not feasible or tolerated within 7-10 days of their procedure [57].

## Complications

In spite of its low associated mortality, significant morbidity is still observed after pancreatic surgery especially in Whipple procedures. A large number of complications are possible, and many are not directly related to the pancreatic operation. These possible complications are shown on Table 6.

### Table 6: Complications after the Whipple operation.

<table>
<thead>
<tr>
<th>Some possible complications after the whistle operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic fistula</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
</tr>
<tr>
<td>Biliary fistula</td>
</tr>
<tr>
<td>Wound infection</td>
</tr>
<tr>
<td>Intraabdominal abscess</td>
</tr>
<tr>
<td>Cholangitis</td>
</tr>
<tr>
<td>Pancreateitis</td>
</tr>
<tr>
<td>Reoperation</td>
</tr>
<tr>
<td>Cardiopulmonary complications</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
</tr>
<tr>
<td>Deep venous thrombosis/pulmonary embolism</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Line infection</td>
</tr>
</tbody>
</table>

## Postoperative Pancreatic Fistula (POPF)

Pancreatic fistula is the Achilles heel of the Whipple operation. A pancreatic fistula increases the morbidity of the operation by leading to other infectious complications (such as wound infection, abscess), delaying resumption of oral diet, prolonging hospital stay, and sometimes requiring reoperation. In large series, pancreatic fistula rate following Whipple is reported as 2-12%. In patients with soft-textured glands or with a pancreatic duct smaller than 3 mm leakage, pancreatic fistula is observed in 20-30% of cases. The definition of pancreatic fistula is controversial. With the aim of creating possible comparisons between published results and arrive at a definition of pancreatic fistula, an international group of pancreatic surgeons met [58]. As a result they came to an agreement and defined a postoperative pancreatic fistula as; a failure of healing of a pancreatic-enteric anastomosis or a parenchymal leak not directly related to an anastomosis. In order to achieve a standardized quantitation, they included a value in their definition; any drain fluid output after postoperative day 3 with an amylase content, three times greater than the serum value constitutes a pancreatic fistula. Furthermore with the aim of categorizing the severity of a pancreatic fistula, they created 3 different grades and predefined ten main criteria are utilized to differentiate each grade. These ten criteria are; elevated drain amylase, persistent drain- age, signs of infection, diagnostic imaging, specific treatments, readmission, critical condition, re-operation, sep-
sis and death. These 3 grades of Postoperative Pancreatic Fistula are explained below in details.

**Grades of Postoperative Pancreatic Fistula (POPF)**

**POPF grade A**
- Requires little change in management or deviation from the normal clinical pathway
- Computed tomographic (CT) scan might not be required and if it is required this often shows no peripancreatic fluid collections
- Oral feeding is not interrupted and general condition of the patients remain well
- The initiation of total parenteral nutrition, antibiotics, or somatostatin analogues are not indicated
- Is not associated with a delay in hospital discharge and is managed frequently by slow removal of the operatively placed drains

**POPF grade B**
- Requires a change in management or adjustment in the clinical pathway
- The peripancreatic drains are usually maintained in place
- Antibiotics are usually required; somatostatin analogues may also be used
- A CT scan is often required and usually shows peripancreatic collection(s) requiring repositioning of the drains
- Often oral feeding is interrupted and the patient is supported with partial or total parenteral or enteral nutrition
- Usually leads to a delay in discharge, or readmission after a previous discharge may be required
- Mostly patients can be discharged with drains in situ and observed in the outpatient setting

**POPF grade C**
- A major change in clinical management
- Clinical intervention should be aggressive
- A CT scan usually shows worrisome, peripancreatic fluid collection(s) that require percutaneous drainage
- There are often associated complications
- The risk of mortality is considered to be high
- Total parenteral nutrition or enteral nutrition, intravenous antibiotics, and somatostatin analogues are required
- The patient’s hospital stay is markedly prolonged. A deteriorating clinical status, together with sep-
sis and organ dysfunction, may require re-explo-
ration for 1 of 3 options:

1. Repairing the site of leakage with wide peri-
pancreatic drainage

2. Conversion to alternative means of pancreatic-
enteric anastomosis (eg, conversion of pancre-
aticojejunostomy to pancreaticogastrostomy)

3. Completion pancreatectomy

Most surgeons agree that not all pancreatic glands are
at the same risk for postoperative fistula formation. Where
the texture of the parenchyma is soft or normal to palpa-
tion and when pancreatic duct is small or normal sized,
the risk of formation of the fistula considered to be high
[59]. There are several measures to apply at the time of
surgery to prevent fistula formation, or decrease morbid-
ity if a fistula develops. For example in recent years, fi-
brin glue sealants have been introduced into the surgical
practice. These are marketed as tissue adhesives to use in
hemostasis, wound closure, and sealing of anastomosis. Ini-
tial reports on the use of fibrin glue in pancreatic resec-
tions suggested that this method is effective in reducing
fistula rates. Multiple randomized controlled trials (RCTs)
followed and a significant difference could not be demon-
strated [60].

The use of octreotide in the prevention and treatment
of postoperative pancreatic fistulas have been extensively
studied in multiple RCTs. Octreotide is a synthetic analog
of somatostatin that has inhibitory effects on the secre-
tory functions of the pancreas. A metaanalysis of all RCT-
on octreotide in the setting of pancreatic surgery shows
that current data support octreotide as an effective tool in
reducing total morbidity and pancreas-related complica-
tions. On the other hand, these effects have not translated
into improved postoperative mortality rates [61]. For that
reason, the use of prophylactic somatostatin and its ana-
logs in pancreatic resections is controversial.

Recent RCTs showed that somatostatin and its analogs
did not reduce the mortality, POPF or other postoperative
complication rates after pancreatic resection [62]. Accord-
ing to the latest consensus meetings, initiation of somato-
statin is indicated before the development of POPF.

For years, surgical drains have been regularly used in
pancreatic surgery. In recent randomized controlled tri-
als, the need for routine drain placement after pancreatec-
tomy has been questioned [63]. However, most pancreatic
surgeons today continue to use surgical drains, and find
them effective in the management of fistulas without fur-
ther necessity for reoperation or percutaneous drainage.

Based on concerns that the pancreatic juice can digest
the pancreaticodigestive anastomosis and/or surrounding
tissue, external or internal drainage of the pancreatic duct
has been considered to decrease the incidence of POPF
formation. Nevertheless, the use of an external drainage
tube leads to difficulties in the daily activities of the pa-
tient and this may delay the discharge process. In order to
successfully prevented POPF formation and avoid these problems, internal stenting was designed. On the contrary, one RCT and four observational studies showed that internal trans-anastomotic pancreatic duct stenting does not decrease the frequency or severity of POPF, the total morbidity, the length of hospital stay or the hospital mortality even in patients with a soft pancreatic texture [64]. Instead, one meta-analysis and three RCTs revealed that external stenting significantly decreased the incidence of POPF formation, independent of the pancreatic texture [65]. As a result in the high risk cases of POPF such as with soft pancreatic texture, using external or internal stenting may be the right approach.

As an alternative, wrapping the anastomosis with omentum/falciform ligament is one of the procedures used to protect the surrounding organs against the pancreatic juice.

This surgical technique is simple and easy for surgeons to perform. However, several reports claim this method does not serve its purpose and it is useless to prevent the POPF related complications [66].

Management of the great majority of pancreatic fistulas is nonoperative. Drains placed at the time of surgery are usually sufficient, but interventional radiology catheters are also an option if undrained collections are identified. Antibiotics may be added if active infection is demonstrated.

Some patients can fail to improve or actually deteriorate clinically during conservative management. Major hemorrhage can be observed in association with a pancreatic fistula. This event usually indicates either ruptures of a pseudoaneurysm of the gastroduodenal artery, or major disruption of the pancreaticojejunal anastomosis. In some cases, embolization by interventional radiology methods can help control this hemorrhage without re-exploration. However, when all conservative measures have failed, reoperation is indicated. Reoperation usually involves peritoneal irrigation, repair, or revision of the pancreatic anastomosis, and wide drainage. Other alternatives, depending on the clinical situation, include conversion to Roux-en-Y pancreaticojejunostomy and total pancreatectomy. In the presence of massive hemorrhage or severe sepsis, total pancreatectomy can be a life-saving procedure.

Delayed Gastric Emptying

Delayed gastric emptying (DGE) without mechanical obstruction can occur in the postoperative period following upper gastrointestinal tract surgery. During postoperative period following pancreatic surgery DGE is especially common therefore this can delay discharge of the patient. In addition to pancreatic fistula and postoperative hemorrhage, DGE is one of the most common postoperative complications after pancreatic surgery, occurring in 19%-57% of patients [67]. DGE occurs after both classic and pylorus-preserving pancreateoduodenectomy. Consensus definition of delayed gastric emptying after pan-
creatic surgery consists of 3 different grades. According to this definition DGE is classified as; Grade A (mild), Grade B (moderate), Grade C (severe). These 3 grades of DGE are listed below in details.

Grade A (mild) DGE
- The nasogastric tube (NGT) is required between the POD 4 and 7
- Reinsertion of NGT may be necessary owing to nausea and vomiting after removal by POD 3
- The patient is unable to tolerate a solid diet on POD 7, but resumes a solid diet before POD 14.

Grade B (moderate) DGE
- The NGT is required from POD 8-14
- Reinsertion of the NGT was necessary after POD 7
- The patient cannot tolerate unlimited oral intake by POD 14, but is able to resume a solid oral diet before POD 21.

Grade C (severe) DGE
- Nasogastric intubation cannot be discontinued.
- NGT has to be reinserted after POD 14
- The patient is unable to maintain unlimited oral intake by POD 21.

DGE directly impacts the patient’s postoperative nutritional status. Poor nutrition can lead to other complications, particularly with relation to healing and immunity.

Therefore, maintenance of caloric intake becomes a priority whenever the diagnosis is DGE. For the most part, DGE is expected to resolve with conservative measures. During this process the surgeon must be very patient, as this condition can take several weeks to improve. Reoperation is rarely necessary.

Hepaticojejunostomy Leakage
Hepaticojejunostomy (HJ) leakage occurs with an estimated frequency between 3 and 8% [68]. The most common clinical signs associated with an HJ leak included; bilious drainage in the drains placed at surgery, leukocytosis, a change in the abdominal examination and fever. Typically, patients presented during the first postoperative week.

Richard et al proposed a grading system of HJ leakage, using the International Study Group on Pancreatic Fistula (ISGPF) system as a sample model.

According to the grading system of Richard et al, there are 3 grades of HJ leakage; Grade A HJ leaks, Grade B HJ leaks and Grade C HJ leaks. These 3 grades of HJ leaks are listed in details below.
Grade A HJLeaks
- Are evident based on the presence of bile in surgically placed drains
- Are not associated with any change in clinical condition
- There is no additional infection
- May be evaluated by sinogram to define the leak and managed with continued abdominal drainage
- The patients typically do not require any additional procedures

Grade B HJLeaks
- Are associated with mild signs of infection, such as a leukocytosis and fever
- A sinogram may be performed to define the leak, and a CT scan is generally necessary to evaluate for undrained collections
- Surgically placed drains can be manipulated or exchanged by an interventional radiologist to optimize drainage in these patients
- Often, an additional abdominal drain is necessary; rarely, a percutaneous transhepatic biliary catheter (PTBD) is required to control a high-output leak and facilitate healing of the anastomosis

Grade C HJLeaks
- Involve an infection that results in significant physiologic derangements or sepsis requiring an increased level of care
- A sinogram often demonstrates a substantial and uncontrolled leak, and early drain outputs are high
- In addition to optimization of abdominal drains, the leaks virtually always require a PTBD
- In patients with severe sepsis reoperative intervention to revise the HJ anastomosis or optimize drainage may also be useful

Finally, all HJ leaks increase length of hospital stay and require several months of abdominal drainage until the leak is completely healed.

Postpancreatectomy Hemorrhage
Although uncommon, hemorrhage after pancreatic resection is a potentially fatal complication that requires timely diagnosis and treatment [69]. The pathogenesis of postpancreatectomy hemorrhage (PPH) is multifactorial. Early PPH within the first 24h after surgery is generally caused by technical failures of inadequate hemostasis and perioperative coagulopathy and usually necessitates immediate relaparotomy. Late PPH after the first postoperative day has a more complex pathogenesis. This may be related to erosion of peripancreatic vessels secondary
to pancreatic fistula formation or ulceration at the site of an anastomosis [70]. Gastrointestinal or intraabdominal hemorrhage occurs in somewhere between 1% to 8% of all pancreatic resections and accounts for 11% to 38% of overall mortality [71] PPH was defined according to the International Group of Pancreatic Surgeons (ISGPS) guidelines considering the following three parameters: (1) time of onset, (2) location, and (3) severity. Early PPH refer to bleeding occurring within 24h and late PPH refers to the bleeding started after 24h postoperatively. The location of bleeding was categorized as intraluminal or extraluminal. Severe hemorrhage required more than 4U of packed cells within 24h, a decrease in hemoglobin of more than 4g/dL, or a need for relaparotomy or interventional angiography to stop the bleeding.

Depending on the severity of hemorrhage, the postoperative bleeding complications can be categorized in three different grades. PPH Grade A, has little or no clinical implication, while PPH Grades B and C lead to critical worsening of the patient’s clinical condition necessitating further treatment. PPH Grade C was defined as potentially life-threatening bleeding [69].

Sentinel bleeding is a small amount of blood loss via abdominal drains or NGT several hours before massive hemorrhage and may be present in 30% to 100% of the cases. Recognizing this event in a timely fashion may prevent severe complications, even death. The management of early PPH usually involves relaparotomy. However, the management of late PPH is usually conservative in hemodynamically stable patients. Endoscopy was frequently undertaken for patients presenting with intraluminal bleeding. However the success rate was not high. Other treatments to achieve definite control of the bleeding, such as surgery or angiographic intervention, may be required. Finally angiographic intervention should be the preferred treatment option in hemodynamically stable patients whereas relaparotomy remains a valid treatment option for hemodynamically unstable patients.

Other Complications

Leakage of the gastroenteric or duodenoenteric anastomosis, is the least common anastomotic complication in pancreatic surgery. The incidence is reported around 1% [72]. Gastroenteric leakage usually led to several additional complications, longer hospital stay, and higher mortality. Its median postoperative day of diagnosis was approximately 1 week after the index operation, and the clinical presentation generally consisted of acute abdomen and the presence of high drain output suspicious of gastric content. Although some patients can be managed by percutaneous drainage alone, operative management is indicated in most patients with gastroenteric leakage, unlike leakage of the pancreaticojejunoanostomy or hepaticojejunostomy.

Postoperative chyle leak in the peritoneal cavity, termed ‘chylous ascites’, is a rare complication following
abdominal surgery. Chylous ascites following abdominal surgery results from surgical damage to the cisterna chyli or its major tributaries [73]. The incidence is between 0.6-3% in different series. The traditional treatment for chylous ascites is dietary control with a medium-chain triglyceride (MCT) diet, intended to reduce the flow of lymph. However, the effectiveness of MCT therapy as a single-modality treatment is low. Therefore, total parenteral nutrition (TPN) combined with therapeutic paracentesis has recently been recommended. Moreover, administration of octreotide, has been advocated for the treatment of chylous ascites, because octreotide reduces fat absorption and decreases lymph fluid excretion. Surgical treatment is rarely required for postoperative chylous leakage. It is generally considered that reoperation should comprehensively depend on daily leakage volume, duration, decreasing tendency, and patient’s general condition. If leakage volume is greater than 1500mL/d or drainage volume remains at high levels (1000mL/d) after fasting, and total parenteral nutrition is supplied for more than one week, or lymphography show a large lymphatic vessel broken parts, surgery should be adopted for chylous leakage treatment.

**Conclusion**

Pancreatic surgery is one of the most complicated operations. Careful study in this field will increase understanding, which will lead to additional protocol improvements to achieve optimal perioperative patient care for the patient with pancreatic disease. Consequently, it is important to understand that a multidisciplinary professional system is crucial to reduce mortality and morbidity in pancreatic surgery.

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