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TOPIC HIGHLIGHT

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Anaesthetic perioperative management of patients with pancreatic cancer

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Abstract

Pancreatic cancer remains a significant and unresolved therapeutic challenge. Currently, the only curative treatment for pancreatic cancer is surgical resection. Pancreatic surgery represents a technically demanding major abdominal procedure that can occasionally lead to a number of pathophysiological alterations resulting in increased morbidity and mortality. Systemic, rather than surgical complications, cause the majority of deaths. Because patients are increasingly referred to surgery with at advanced ages and because pancreatic surgery is extremely complex, anaesthesiologists and surgeons play a crucial role in preoperative evaluations and diagnoses for surgical intervention. The anaesthetist plays a key role in perioperative management and can significantly influence patient outcome. To optimise overall care, patients should be appropriately referred to tertiary centres, where multidisciplinary teams (surgical, medical, radiation oncologists, gastroenterologists, interventional radiologists and anaesthetists) work together and where close cooperation between surgeons and anaesthesiologists promotes the safe performance of major gastrointestinal surgeries with acceptable morbidity and mortality rates. In this review, we sought to provide simple daily recommendations to the clinicians who manage pancreatic surgery patients to make their work easier and suggest a joint approach between surgeons and anaesthesiologists in daily decision making.

Key words: Pancreatic cancer; Pancreatic surgery; Perioperative anaesthesia management

Core tip: Currently, the only curative treatment for pancreatic cancer is surgical resection. However, this type of surgery is still burdened by considerable morbidity due to its complexity and to the type of referred patients (elderly and with many co-morbidities). We believe that anaesthetic management with proper surgical approaches can play a key role in the outcome of the patient. Simple perioperative precautions in anaesthetic management (patient risk assessment, fluids management, prevention of surgical site infection, thromboprophylaxis, intraoperative ventilation, and intensive postoperative management) can help to ensure that these surgical operations are performed with reasonable assurance.

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INTRODUCTION

Pancreatic cancer (PC) is the fourth leading cause of

Table 1 A schematic representation of the integrated management of perioperative patients undergoing surgery for pancreatic cancer

Preoperative	Intraoperative	Postoperative
Informed patient consent	Combined general and epidural analgesia	Early nasogastric tube, catheter and drain removal
Preoperative risk assessment	Prevention of surgical site infection: Antimicrobial prophylaxis Avoid hypothermia Glucose control	Early oral nutrition/glycaemic control/goal-directed fluid therapy Pain relief/non-opioid oral analgesia
Evaluation and optimisation of preoperative physical conditions and medications	Blood transfusion management	Intensive postoperative ambulation and prevention of venous thromboembolism
Nutritional status	Intraoperative fluid management	Intensive respiratory rehabilitation
Risk stratification, rationale for thromboprophylaxis, and recommendations	Optimisation of intraoperative ventilation Intraoperative thromboprophylaxis	Intensive postoperative management

Modified from Grade *et al*[10].

cancer-related death in the United States and the sixth in Europe, with the lowest survival rate for any solid cancer worldwide[1]. It is the most lethal type of digestive cancer and exhibits a five year survival rate of 5% with a range that is correlated with staging and location. The main reason for this extremely poor prognosis is that less than 15% of patients are diagnosed with resectable tumours[2]. Currently, the only curative treatment for PC is surgical resection, although even for resectable tumours, cure is still rare (5-year survival rate of approximately 15%-20%)[3].

Pancreatic surgery represents a challenging and technically demanding major abdominal procedure that occasionally results in a number of pathophysiological alterations during the early postoperative period that account for increased rates of morbidity and mortality.

Systemic, rather than surgical complications, cause the majority of PC-related deaths[4]. More than 80% of PCs are diagnosed in patients older than 65 years. Many PC patients are or have been heavy smokers[5,6], and nearly 80% of PC patients have either frank diabetes or impaired glucose tolerance[7]; venous thromboembolism remains a major complication of PC[8]. For these reasons, PC patients who undergo a major abdominal surgery are at increased anaesthesiological risk. In the light of these issues, it is important to refer these patients to centres with a high volume of operations where a multidisciplinary approach is applied to improve the overall outcome. Moreover, careful patient selection is fundamental.

In this setting, the anaesthesiologist plays a crucial role during preoperative evaluation, which together with a proper surgical approach and a concerted effort with medical physicians, radiation oncologists, gastroenterologists and interventional radiologists is crucial for a favourable perioperative outcome[9]. Patient outcome can be significantly influenced by anaesthesiological management (Table 1), starting with patient stratification and selection, continuing throughout the surgical operation and finishing with postoperative care [intensive care unit (ICU), recommendations for the ward][10].

PREOPERATIVE MANAGEMENT

Informed patient consent

Despite recent developments in operative technique and postoperative care, pancreatic surgery remains associated with high morbidity and mortality. Postoperative complications such as primarily pancreatic fistula, haemorrhage, abscess, and delayed gastric emptying still occur at a frequency of 30% to 60%, resulting in a mortality rate of 1% to 5%[11]. For this reason and due to the lethality of the pancreatic cancer despite surgical treatment, the patient should be informed about the therapeutic procedure and any potential complications or disabilities to facilitate a conscious involvement in the decision-making process.

In the case of patients of advanced age who require pancreatic surgery, formal mental status testing can help determine whether a patient can be considered capable of making this type of decision.

Dementia is an extreme predictor of poor outcome, exhibiting surgical mortality rates that are increased by 52%[12]. The decision to classify an elderly patient eligible for surgery cannot exclude preoperative mental status.

Preoperative risk assessment

A complete history, physical, laboratory examinations, and an assessment of the surgical risks should be included in the preoperative evaluation of an elective surgery.

Currently, the definition of preoperative risk remains vague and difficult to standardise, as it is influenced by many variables attributed to patient- and surgery-specific variability[13]. Recently, a variety of scoring systems has been developed, and the Physiologic and Operative Severity Score for the Enumeration of Mortality and morbidity (POSSUM) model by Copeland *et al*[14] was recognised as the most effective for general surgery[15]. This model, which uses scores relating to 12 physiological and 6 operative variables, was developed to postoperatively predict 30-d mortality and morbidity. The application of the predictive POSSUM and P-POSSUM (Portsmouth modification of POSSUM)[16] models to cases of pancreatic surgery has generated conflicting results. The implementation of this scoring system in the routine practice has proven to be difficult, and a recent review by Wang *et al*[17] has found POSSUM to overpredict postoperative mortality. Despite these limitations, there is still a role for POSSUM as a useful tool in pancreatic surgery. Individual POSSUM scores should not preclude pancreatic resec-

tion in clinical practice but might help surgeons modify expectations of postoperative outcomes[18].

Due to the limitations of the POSSUM model, more trials are needed to adequately evaluate this scoring system in predicting postoperative mortality for pancreatic surgery.

Evaluation and optimisation of preoperative physical conditions and medications

A growing number of old patients benefits from a surgical procedure[19]. Age is an independent risk factor of postoperative mortality and postoperative complications and can cause a gradual progressive loss in the biological reserves for maintaining physiological homeostasis under stress. In addition, an increasing number of patients present with one or more age-related chronic conditions, which further decrease their ability to respond to stress. Cardiac and pulmonary diseases are the most frequently observed co-morbidities that anaesthetists and surgeons must manage during this complex surgery.

A complete history of prior medical and surgical conditions and a full medication list are particularly important[20,21].

Cardiovascular risk evaluation: Cardiovascular complications are among the most common and significant postoperative problems in elderly patients. A practical guideline for perioperative cardiovascular evaluation for non-cardiac surgery has been proposed by the American College of Cardiology and American Heart Association Task Force[22]. Patients should be assessed using an approach that considers clinical predictors, the risk of the proposed operation and the functional capacity.

Ageing is accompanied by increased vascular and ventricular stiffness, diastolic dysfunction and an increased risk of heart failure[23]. Diastolic dysfunction even with a normal or supranormal ejection fraction might elicit a significant effect on the perioperative outcome and management of elderly patients[12]. Diastolic dysfunction might significantly affect perioperative haemodynamics, response to fluid shifts, anaesthetic drugs and other perioperative medications.

Patients with cardiovascular diseases are sensitive to haemodynamic instability and often require increased filling pressures to generate an adequate cardiac output. The anaesthetist must carefully manage fluids during the operation to avoid overload or rapid volume administration. Moreover, the anaesthetist must maintain a normal haemoglobin value (Nair *et al*[24] demonstrated that anaemia was strongly associated with diastolic dysfunction in patients with coronary artery disease) and, if possible, must choose volatile anaesthetics that appear to improve diastolic parameters (in contrast to propofol, which elicits the opposite effect) as measured by echocardiography[25]. Thoracic epidural analgesia should be strongly suggested, not only for pain management and for decreasing respiratory complications but also because its use appears to improve cardiac function by improving the diastolic characteristics of the left ventricle[26,27].

Prophylactic perioperative β-blockade: In general, cardiovascular medication should not be discontinued prior to surgery. In the perioperative setting, β-blockers are not contraindicated in patients with diastolic heart failure and should be continued in patients with systolic heart failure. However, caution is warranted with the acute administration of β-blockers in situations of decompensating systolic heart failure. Nonetheless, given the risk of acute withdrawal, β-blockade in patients with coronary artery diseases or coronary artery disease risk factors should not be discontinued preoperatively. Rather, perioperatively increasing the dosage of the patient's β-blockade regimen would most likely be beneficial[28-30].

If a patient who is scheduled for elective pancreatic surgery requires a new prescription, it should be started at least 1 mo prior to the procedure to allow for dose adjustment[31,32].

Pulmonary risk evaluation: Pulmonary complications such as pneumonia, failure to wean, and postextubation respiratory failure represent the second most frequent types of postoperative complication following wound infection, with an estimated incidence rate ranging from 2.0% to 5.6% following surgery[33,34]. Pulmonary disease increases the risk of postoperative complications, accounting for 40% of postoperative complications and 20% of deaths[35]. Age-related changes, such as increased closing volumes and decreased expiratory flow rates can predispose older patients to pulmonary complications.

Some postoperative pulmonary complication (PPC) predictors after pancreatic surgery are summarised in Table 2 (modified from Canet *et al*[36]).

Identifying the patients who are at high risk for PPCs, can help the anaesthetist to design individually tailored management approaches[37-39]. Pharmacologic measures for managing these complications are either unavailable or limited, and as a result, treatments must be based on physical therapy and respiratory support ventilation.

Finally, the ability to predict PPCs would enable clinicians to give patients more precise risk assessments, thereby facilitating their decision making.

Nutritional status and mechanical bowel preparation

The prevalence of malnutrition is high in patients who are submitted for surgery and ranges from 35% to almost 60%[40]. Malnutrition has been consistently associated with impaired immunity[41] and can lead to increased complications, such as pressure ulcers, delayed wound healing, increased risk of infections, impaired muscular and respiratory functions[42], as well as increased mortality and poor clinical outcomes.

Nutritional status should be determined because nutritional deficiencies are common in patients who have undergone pancreatic resection for malignant tumours. Because malnutrition is potentially reversible with appropriate nutritional support, the early identification of high-risk patients is crucial, and preoperative malnutrition screening is required to identify and to treat the malnutrition[43]. Recently, the routine screening of patients to iden-

Table 2 Perioperative clinical predictors of postoperative pulmonary complication in pancreatic oncological surgery

Patient-related factors	Surgery-related factors	Preoperative testing-related factors
Congestive heart failure	Abdominal surgery	Serum albumin concentration < 2.5 g/dL
ASA score > 2	Surgery duration > 3 h	Anaemia (Hb < 10 g/dL)
Age > 65 yr	General anaesthesia	Low SpO2
Chronic obstructive pulmonary disease	Transfusions	Chest X ray
Functional dependence	Prolonged hospitalisation	
Weight loss		
Impaired sensorium		
Cigarette smoking		
Respiratory infections within the past month		

Modified from Canet *et al*[36]. ASA: American Society of Anesthesiologists.

tify risk of malnutrition has been recommended by many national, international, and specialist organisations[44,45]. The malnutrition universal screening tool (MUST) for adults was recently validated by several studies, which have demonstrated that as a screening procedure, MUST is rapid and easy to use[46,47].

The MUST appears to be a valid and easy screening tool for pancreatic surgery[20], which can identify patients at high risk for major complications and death. Furthermore, the MUST can prompt the implementation of effective nutritional interventions to reduce poor outcomes and thereby optimise the use of postoperative critical care beds and hospital resources.

As soon as malnutrition is recognised, preoperative nutritional supplements should be provided when possible. This supplementation can include high-energy foods, vitamins, enteral feedings, or, if necessary, total parenteral nutrition.

Mechanical bowel preparation

"Enhanced recovery" or "fast-track" (FT) programmes, which were first developed by Kehlet[48], are structured interdisciplinary strategies that have been introduced to optimise peri-operative care and to accelerate post-operative recovery[49]. A major intervention principle of this approach is the avoidance of preoperative mechanical bowel preparation (MBP), which has been employed as a preventative measure in gastrointestinal surgery for more than a century as an essential factor for avoiding infectious complications and anastomotic dehiscence. FT programmes, which exclude MBP, have been proposed more often in other surgical fields (elective colorectal, gastro-oesophageal and aortic surgery) and rarely have been applied to liver and pancreatic surgery[50]. The application of MBP in this type of surgery has been evaluated by limited studies (a retrospective case-control study by the Jefferson University[51] and a review by Salvia *et al*[52]), which have shown that it did not improve perioperative outcomes. At our institution, MBP has been excluded from clinical practice in pancreatic surgery. A recent review examined and compared the application of FT protocols with standard care in elective liver and pancreatic surgeries, showing that FT programmes can enhance post-operative recovery and reduce the length of hospital stays with no increase in adverse events, such as re-admissions, morbidity or mortality[53,54]. The avoidance of MBP, together with other measures including the application of epidural analgesia, the prevention of intra-operative hypothermia, fluid restriction, post-operative nutritional care and early mobilisation, collectively represent essential elements of a FT programme that is warranted for complex surgical operations such as pancreatic resection[55,56]. In our experience FT programmes for hepatopancreatic resections appear to be safe and associated with a reduction in the length of hospital stays.

Risk stratification, rationale for thromboprophylaxis, and recommendations

In patients undergoing general and abdominal-pelvic surgery, the risk of venous thromboembolism (VTE) varies depending on both patient- and procedure-specific factors[57]. Pancreatic cancer is among the most common malignancies associated with thrombosis, as it occurs in 50% of total patients[58]. Prophylaxis against postoperative venous thromboembolism should be tailored to the patient's level of risk. A model (the Caprini score) that can potentially be used for such purposes estimates VTE risk by adding points for various VTE risk factors[59].

Pharmacological prophylaxis reduces the risk of pulmonary embolism by 75% in general surgical patients and by 57% in medical patients[60]. The use of low-molecular-weight heparins (LMWHs) to prevent thrombotic events in these patients is a common and well-documented practice.

Current recommendations strongly advise effective and preventive strategies for all hospitalised patients who are defined as moderate to high risk for VTE and are awaiting pancreatic surgery.

LMWHs appear to be effective and are potentially associated with a lower risk of bleeding when the first dose is administered 12 h preoperatively[57,61]. We recommend the administration of LMWH from the day prior to surgery to all patients scheduled for pancreatic cancer surgery.

In the case of patients who are receiving anticoagulants or antiplatelet therapy and require an elective surgery or procedure, the actual guidelines addressing their management are underlined in Table 3 and are modified from Douketis *et al*[62].

INTRAOPERATIVE MANAGEMENT

Combined general and epidural anaesthesia

The use of thoracic epidurals is widespread for intraoperative and postoperative analgesia. Thoracic epidural anaesthesia (TEA) reduces sympathetic activity, thereby influencing the perioperative function of vital organ systems. Thoracic epidural anaesthesia has been used widely to provide excellent pain relief, to attenuate the catabolic

Table 3 Guidelines on the prophylaxis of venous thromboembolism and antiplatelet and anticoagulant management adjusted according to recent guidelines

In patients receiving bridging anticoagulation with a therapeutic-dose Ⅳ of unfractionated heparin, treatment is recommended to be stopped no later than at 4 to 6 h prior to surgery
In patients receiving bridging anticoagulation with a therapeutic-dose of LMWH, the last preoperative dose of LMWH is recommended to be administered at approximately 24 h prior to surgery instead of at 12 h prior to surgery
In patients receiving bridging anticoagulation with a therapeutic-dose of LMWH and are undergoing high-bleeding-risk surgery, resumption of the therapeutic dose of LMWH is recommended at 48 to 72 h after surgery instead of within 24 h following surgery
In moderate-to-high-risk patients receiving acetylsalicylic acid who require non-cardiac surgery, treatment with acetylsalicylic acid is recommended to be continued around the time of surgery instead of discontinued at 7 to 10 d prior to surgery
In patients with a coronary stent who require surgery, deferment of surgery is recommended at 6 wk or 6 mo after the placement of a bare-metal or drug-eluting stent, respectively, instead of initiating surgery during these time periods
In patients requiring surgery within 6 wk or 6 mo of the placement of a bare-metal or drug-eluting stent, respectively, continuing perioperative antiplatelet therapy is recommended instead of stopping therapy at 7 to 10 d prior to surgery

Modified from Douketis *et al*[62]. LMWHs: Low-molecular-weight heparins.

response to abdominal surgery, to lower the incidence of pulmonary morbidity, to decrease the cardiac metabolic demand, to reduce the risk of thromboembolic complications, to promote the recovery of intestinal function and to minimise motor blockade[63,64]. Moreover, epidural anaesthesia and mild hypercapnia have been shown to increase subcutaneous tissue oxygenation[65].

The combination of general anaesthesia and thoracic epidural anaesthesia has become the technique of choice at many institutions for major abdominal surgery[66,67].

Recent studies have suggested that for some types of cancer, TEA might also reduce the rate of recurrence after surgical resection. The possibility of reducing tumour recurrence makes the combination of general anaesthesia and TEA even more appealing, despite the existence of certain contraindications[68,69].

TEA represents a powerful tool that is available to anaesthesiologists for perioperative intervention in pancreatic surgery. At our University Medical Centre, we strongly address its use in the context of multimodal intervention.

Prevention of surgical site infection

Surgical site infections continue to represent a substantial source of morbidity and mortality in the surgical patient population. They are the second most common cause of nosocomial infection after urinary tract infections and account for approximately 17% of all hospital-acquired infections[70].

Increasing evidence indicates that anaesthesiologists play a prominent role in the prevention of surgical site infections. Anaesthesiologists are involved in the administration of antibiotics, in the use of supplemental oxygen, in the maintenance of normothermia and normoglycaemia, in the perioperative fluid management and in the administration of blood transfusions[71,72]. Therefore, decreasing surgical site infections depends on the optimisation of some perioperative conditions, which are generally controlled by anaesthesiologists.

Antimicrobial prophylaxis

The anaesthesiologist can play a simple but effective role in the prevention of surgical site infections by ensuring the administration of appropriate antimicrobial prophylaxis[73,74].

Current recommendations state that the infusion of the first dose of drug should begin within 30-60 min of incision. This period can be lengthened to 120 min for drugs such as vancomycin, where high infusion rates have been associated with complications[75]. The drugs used should be defined in advance for each intervention, including alternatives in the event that the patient presents with any contraindication for the frontline antibiotics. The determination of the ideal preoperative antibiotic therapy for a patient who is awaiting pancreatic surgery requires efforts by a multidisciplinary team (anaesthesiologist, surgeon and microbiologist). A proper and effective antimicrobial prophylaxis should be based upon the application of a standard protocol and quality management[76].

Concerning the duration and dosage of prophylaxis, the guidelines generally recommended a single standard intravenous therapeutic dose of antibiotic in the majority of procedures. Repeated doses have only been indicated in special circumstances such as prolonged surgery with a duration longer than the half-life of the antibiotic used or cases of major blood loss. This recommendation is based on published evidence, which suggested that the administration of short-duration prophylaxis is equally effective as longer-duration prophylaxis in the prevention of surgical site infections[77,78]. It is advisable to administer at least two antibiotic doses during pancreatic surgery.

Avoid hypothermia

Mild perioperative hypothermia (core body temperature 34-36 ℃) is commonly observed in surgical patients. The complications of mild perioperative hypothermia have been studied extensively and include increased duration of hospitalisation, increased intraoperative blood loss and transfusion requirements, increased adverse cardiac events, and an increase in patient thermal discomfort in the recovery room[79,80]. The effects of mild hypothermia on surgical site infections have also been studied. The major relation between hypothermia and increased surgi-

cal site infections is thought to be a decrease in subcutaneous tissue perfusion mediated by vasoconstriction[81,82]. The reduced oxygenation of the wound is responsible for reduced oxidative killing elicited by neutrophils and for the reduced production of superoxide radicals for any given oxygen tension[80].

Intraoperative core temperature monitoring (oesophageal temperature probe) and adequate control of body temperature are essential during pancreatic cancer surgery[83]. Heat loss during the first hour of anaesthesia is generally a result of the redistribution of core-to-peripheral temperature gradients caused by an anaesthetic-induced decrease in vasoconstriction. The exposure of the large bowel, significant amounts of fluids administered, and long surgical procedures represent other causes of intraoperative hypothermia. Actively pre-warming patients for 2 h prior to the induction of either general or regional anaesthesia[80] using forced-air warming blankets together with fluid-warming systems represents an important way to keep patients normothermic[84].

Glucose control

Hyperglycaemia is associated with an increased risk of morbidity and mortality[85]. Several studies have shown the negative effects of hyperglycaemic phases during hospitalisation on the rate of nosocomial infections, length of hospital stay and mortality[71,86]. In a recent trial, the use of insulin infusions to maintain serum glucose at less than 110 mg/dL in critically ill patients decreased the mortality rate from 8.0% to 4.6%, regardless of diabetic status[87]. In subsequent studies, the concept of intensive glucose control was modified towards less-extreme blood glucose levels because of dangerous hypoglycaemic episodes that were attributable for worse patients outcomes than that originally reported[88,89]. Intraoperative glucose control should be a standard practice during long and complex surgical procedures to reduce perioperative complications.

The optimal glucose level during the perioperative period has not been prospectively investigated, and the available data from recent reports do not indicate a specific threshold for the treatment of hyperglycaemia. There is some evidence that keeping glucose levels within a range of 110-180 mg/dL and not limiting the treatment to values higher than 200 mg/dL is safe and appropriate.

It is important not only to limit glucose control during the intraoperative period but also to continue insulin infusion during the postoperative period. The frequent and precise measurement of glycaemia must become a standard of pancreatic cancer patient management both during surgical procedures as well as during the postoperative period[90].

Blood transfusion management

Several published studies have demonstrated how blood product transfusions increase the postoperative risk of infection[91,92].

Published guidelines generally concur that although transfusions are not beneficial when the haemoglobin concentrations are greater than 100 g/L, they confer benefit when the haemoglobin concentrations are less than 60-70 g/L. Studies that have described transfusion management in Jehovah's witnesses have shown that morbidity and mortality only increase postoperatively for each gram of decrement when the haemoglobin concentration is less than 70 g/L[93]. Patients with cardiovascular diseases exhibit a significantly increased rate of postoperative mortality, and for this reason, the transfusion trigger should be different for patients with or without cardiovascular disease[94,95]. Although multiple trials have assessed the effects of transfusion thresholds on patient outcome, the literature is insufficient for defining a transfusion trigger in surgical patients with substantial blood loss. In the light of recent findings, the transfusion management of surgical patients should be patient specific and should not be based on arbitrary laboratory values but guided by patient covariables[96-99]. As underlined by the recent guidelines on perioperative bleeding management of the European Society of Anaesthesiology, we suggest a target haemoglobin concentration of 7-9 g/dL and the guidance of transfusions based on levels of serum lactate, base deficit, and central venous oxygen saturation[100].

Intraoperative fluid management

Optimal perioperative fluid management remains highly challenging, particularly in patients undergoing major abdominal surgery[101-103]. Perioperative physicians generally administer intravenous fluids to replace fasting deficits, third space losses, and blood loss to maintain adequate cardiac output, blood pressure, and urine output.

Fluid excess can have a negative impact on cardiac, pulmonary, bowel function and wound healing, predisposing the patient to tissue oedema and anastomotic breakdown[104,105]. In contrast, excessive fluid restriction can expose the patient to hypovolaemia and hypoperfusion[106]. Surgery causes inflammation and a corresponding release of mediators that can induce local tissue oedema[107]. Anaesthetists generally manage perioperative fluid administration by using unmonitored fixed fluid regimens and estimating fluid loss.

In recent years, restrictive fluid management has replaced this approach, and the concept of fast-track surgery has challenged the traditional administration of large amounts of fluids during surgery[108,109].

These findings have prompted fervent discussion on how liberal or restrictive perioperative fluid management should be applied, and several randomised controlled trial have attempted to settle this issue[104,108,110,111].

Due to the lack of consensus on the optimal implementation of fluid management, a new and more precise approach based on goal-directed fluid therapy and individualised fluid administration has been developed[103]. Goal-directed fluid optimisation has markedly increased tissue oxygen tension and microcirculatory perfusion in both healthy and perianastomotic tissues compared to the restricted fluid strategy[106,112,113].

Central venous pressure (CVP) remains the most

widely used clinical marker of volume status, despite numerous studies indicating no association between CVP and circulating blood volume[114]. Because of this limitation, central venous and pulmonary artery occlusion pressures, which are the only variables for guided fluid therapy and optimised preload, are not recommended. Dynamic parameters such as stroke volume variation or pulse pressure variation provide a more favourable prediction of fluid responsiveness. Individualised goal-directed fluid therapy, particularly oesophageal Doppler-guided fluid optimisation, has been shown to improve patient outcomes and to reduce the length of hospital stays compared with conventional fluid replacement[115]. Doppler-guided fluid boluses appear to improve clinical outcomes, particularly in elderly and frail patients[116,117]. This method, however, cannot be universally performed for practical and financial reasons[118].

Using a "goal-directed" approach, it is generally possible to replace lost plasma, whereas the extracellular compartment cannot currently be monitored. Therefore, losses from the latter should be replaced based on the protocol suggested by Chappell *et al*[101], which involves the substitution of insensible perspiration with 1 mL/kg per hour during abdominal surgery and does not include the possibility of primary fluid consumption by the third space, the existence of which is denied[119].

The optimal solution for volume replacement and optimisation remains an ongoing issue of heated debate. The goal of perioperative fluid management is to maintain fluid balance and to minimise the possible risks by choosing the right fluid at the right time.

Colloids are criticised because of their ability to diffuse into the interstitium, making further extravasation more likely[120], because of the cumulative and persistent effects related to their infusion[121] and, finally, because of safety concerns. Recent studies of the potential increase in the risk of bleeding and acute kidney injury following the application of various colloids have shown that the use of hydroxyethyl starch appears to be associated with an increased need for dialysis[122] and might even increase mortality in patients with sepsis[123].

Current evidence suggests that beyond fluid composition, the timing and volume of the administered fluid represent two additional factors that are likely to influence perioperative patient outcome. For patients with mild-to-moderate volume deficits, crystalloids are still the first choice. In the case of severe volume depletion, we recommend starting fluid resuscitation with a colloid to rapidly reverse volume deficits and ensure oxygenation and then to switch to crystalloids once the patient approaches euvolaemia.

Goal-directed fluid management enables appropriate use of fluids, vasopressors, and inotropes, and results in improved outcomes. The vasodilatatory effect of anaesthetic cannot be ignored and must be expected to terminate at the end of surgery. Treating vasodilatation with crystalloids or colloids can be a mistake in all euvolaemic patient, whereas vasopressor infusion during surgical operation can help in avoiding excessive fluid overload[124,125].

Optimisation of intraoperative ventilation

Postoperative pulmonary complications following major upper abdominal surgery increase morbidity, mortality, the length of hospital stay and costs[33]. Reduced lung inflation represents one of the basic mechanisms of postoperative pulmonary complications. The adjustment of the body positioning from upright to supine itself can reduce the resting lung volume by approximately 0.8-1.0[126]. The additive effect of supine positioning, general anaesthesia, and abdominal incisions significantly reduces functional residual capacity and increases airway resistance. In addition, during the induction of anaesthesia, most of the general anaesthetics further reduce functional residual capacity. The combination of these effects predisposes patients to atelectasis with the risks of hypoxemia and infection. Additionally, postoperative pain and the use of analgesics can contribute to a reduced tidal volume and impaired clearing of secretions, depending on adequate coughing and deep breathing[126,127].

Mechanical ventilation is mandatory in patients undergoing general anaesthesia. High tidal volumes can overdistend non-injured lungs, particularly in non-dependent lung tissues. The non-aerated atelectatic lung regions are prone to repeated collapse and re-expansion of the alveoli, causing shear stress and diffuse mechanical damage of the alveoli. During surgical procedures, both phenomena can induce stress in non-injured lung tissues, triggering local inflammation[128,129]. Retrospective and prospective studies have shown the potential beneficial effects of reduced tidal volumes in patients who are on short-term mechanical ventilation following surgery[130]. Protective mechanical ventilation using reduced tidal volumes can accordingly reduce ventilator-associated lung injury. The application of positive end expiratory pressure (PEEP) can prevent alveolar collapse and atelectasis formation, and recruitment manoeuvres can support the beneficial effects of PEEP during short-term ventilation[131]. Effective anaesthesiological management during pancreatic surgery should involve the application of a protective ventilation strategy (lower tidal volumes < 8 mL/kg, PEEP = 6-12 mmHg and recruitment manoeuvres) to improve respiratory function during the postoperative period following abdominal surgery and to reduce the clinical signs of pulmonary infection during the postoperative period[132].

Intraoperative thromboprophylaxis

The use of LMWHs to prevent thrombotic events in these patients represents a common and well-documented practice. Effective pharmacological thromboprophylaxis includes the administration of LMWH from the day prior to the surgery. In addition to this useful approach mechanical prophylaxis including graduated compression stockings and intermittent pneumatic compression is highly recommended during the surgical operation and during the postoperative period until the risk of bleeding has diminished and the application of new pharmacological prophylaxis might be initiated[57,60].

Thromboelastography can play a potential role, despite its limitations, as a valuable tool for the evaluation of the entire perioperative coagulation process and hypercoagulability changes, as well as for increasing patient safety through more effective management of antithrombotic therapy[133,134].

POSTOPERATIVE MANAGEMENT

Over the past 20 years, surgery and anaesthesia for patients undergoing abdominal surgery have undergone immense development. A novel concept of perioperative patient care following surgical abdominal procedures has emerged. Fast track programmes, a new concept of enhanced recovery after surgery and the implementation of multimodal rehabilitation, have heavily influenced this modern change, optimising perioperative care, accelerating recovery and reducing hospital stays and costs. The objective of this integrated approach between surgeon, anaesthetist, nurses and physiotherapist is to reduce the impact of surgery on patient homeostasis. The main pillars of this new management are those shared by fast track surgery and can be summarised as follows: (1) reduction of surgical invasiveness (early removal of drains, nasogastric tube, small incisions, pharmacological stimulation of the gut); (2) pain relief/non-opioid oral analgesia; (3) early oral nutrition/goal-directed fluid therapy; (4) intensive postoperative ambulation and prevention of venous thromboembolism; and (5) intensive respiratory rehabilitation.

All of these basic points, combined with the prevention of intraoperative hypothermia, neural blockades[135], maintenance of euglycaemia, and the development of goal-directed fluid therapy contribute to the reduction of surgical stress.

A systematic review of the literature regarding perioperative care in pancreatic cancer surgery has revealed a limited number of studies providing low levels of evidence[50,54,136]. Despite their potential weaknesses, the studies detailed above have demonstrated that implementation of fast-track peri-operative care pathways is feasible in pancreatic surgery and can be associated with reduced length of stay, reduced relevant hospital costs and no increase in morbidity, 30-d mortality or re-admission rates.

Early nasogastric tube, catheter and drain removal

Nasogastric tube: Nasogastric tubes have been routinely used following abdominal surgery until normal bowel function is restored, following the notion that gastric decompression resulting from decreased air and fluid accumulation can prevent abdominal distension, nausea and vomiting. Many studies have subsequently questioned this practice, advising against its routine use. In fact, prophylactic nasogastric tube aspiration is associated with pulmonary complications[137] and significant patient discomfort. A recent study on the implementation of fast-track recovery pathways in pancreatic surgery[138] has underlined the advantages of the early removal of nasogastric tubes and early oral feeding in terms of incidence of delayed gastric emptying and earlier bowel activity. Given the risk of pulmonary complications, significant patient discomfort and lack of benefit associated with prophylactic nasogastric tube aspiration, this practice should not be routinely used[139,140].

Consistent with a recent study, in our daily practice, we remove nasogastric tubes on postoperative day 1 only if the tube drainage amount is less than 300 mL or at the end of surgery in cases of distal pancreatectomy which makes delayed gastric emptying less frequent[52].

Abdominal drains: The presence of an abdominal drain represents a significant impediment to achieving early and appropriate levels of mobilisation. Several randomised trials have not found any benefit of prophylactic drains after surgical operations, such as cholecystectomy[141], colorectal surgery[142] or hepatectomy[143]. Rather, these prospective randomised studies found that routine drainage resulted in an increased frequency of complications and no difference in outcome.

Because pancreatic surgery is associated with high rates of morbidity, the purpose of prophylactic drainage is to prevent fluid collection and to aid in the early detection of anastomotic leak and associated haemorrhage. Following pancreatectomy, the use of a prophylactic drain is supported by the belief that the early detection of pancreatic fistulae through the measurement of amylase in the draining fluid will allow for the efficient management and the avoidance of major complications[144]. Despite reports of randomised, control trials and cohort studies that do not support the use of drains, most surgeons routinely place prophylactic intraperitoneal drains at the time of pancreatic resections[145,146]. Evidence-based practice guidelines for drain management during pancreatectomy remain to be established despite the remarkable number of studies that are available to help guide practice.

At our University Hospital, abandoning drainage during pancreatic surgery is believed to be unsafe, and according to Kaminsky *et al*[146], it is reasonable to suggest a practice of selective drainage based on the presence of risk factors. The presence of soft pancreas texture, a small pancreatic duct diameter, increased intraoperative blood loss (> 200 mL) and prolonged operative time are risk factors that reflect abdominal drains. In the case that patient is doing well and the drain amylase levels are below 5000 U/L, drains [on postoperative day 1 (POD 1)] can be safely removed on POD 3 in patients with low risk of pancreatic fistulae.

Early oral nutrition

The restoration of normal gastrointestinal function to allow adequate food intake and rapid recovery is one of the primary objectives of postoperative care. A meta-analysis of controlled trials of early enteral or oral versus 'nil by mouth' feeding after gastrointestinal surgery indicated no clear advantage to continued patient fasting after the elective gastrointestinal resection[147].

Concerning nutrition, studies have clearly found that

allowing eating/drinking until late the day prior to surgery and commencement of eating/drinking soon after surgery has many advantages[148,149]. Through the earlier intake of fluids and solids, the gastrointestinal system is less affected with an earlier initiation of normal intestinal activity.

An interesting review analysing which feeding routine was more favourable following pancreatoduodenectomy revealed no consensus in terms of postoperative nutrition of patients who had undergone pancreatic surgery. Current European guidelines recommend routine enteral feeding after pancreatoduodenectomy, whereas the American guidelines do not. Gerritsen *et al*[150] concluded that there is no evidence to support routine enteral or parenteral feeding after pancreatoduodenectomy, whereas the oral diet appears to be the best feeding strategy.

At our University Hospital, it is common to allow the patient to take clear liquids from POD 1 but not before 6 h postoperatively and a light diet from POD 2, in the absence of any complications. In patients at risk of postoperative complications such as pancreatic fistulae or abdominal collections, we advocate the use of combined parenteral and enteral nutrition[52].

Total pancreatectomy and postoperative glycaemic control

Total pancreatectomy, usually performed for the treatment of multifocal disease or in case of atrophic, soft, friable remnant pancreatic tissue is responsible of endocrine and exocrine insufficiency. In addition to the absence of insulin, the endocrine abnormalities accompanying total pancreatectomy include both glucagon and pancreatic polypeptide deficiencies, which appears to play a key role in the increased hepatic insulin resistance observed in pancreatogenic diabetes[151]. Moreover, following pancreatectomy, insulin receptors are upregulated peripherally, rendering patients uniquely sensitive to hormone replacement[152].

This type of diabetic condition is defined "pancreatogenetic" diabetes and is often considered to be different from type 1 and 2 diabetes. This diabetic state is commonly described as "brittle", as a result of enhanced peripheral insulin sensitivity, decreased hepatic insulin sensitivity and reduction of glucagon secretion. The resulting labile glycaemic control is characterized by periodic episodes of both hyper and hypoglycaemia[153,154].

In recent years, studies have shown that diabetes following total pancreatectomy is not necessarily associated with poor glycaemic control, and the majority of cases exhibit equivalent biochemical controls compared to the normal type 1 diabetic population[155,156].

Recently, the development of accurate, continuous blood glucose monitoring devices, particularly closed-loop systems, for computer-assisted blood glucose control in the intensive care unit have been reported to assist in obtaining favourable glycaemic control in patients with pancreatogenic diabetes following pancreatic resection[157].

The hyperglycaemia induced by surgical stress cannot be controlled using the conventional sliding scale method[158], whereas the perioperative use of an artificial endocrine pancreas enables strict glycaemic control of euglycaemia without severe hypoglycaemia[159,160].

Modern pancreatic enzyme formulations have improved exocrine insufficiency, facilitating glycaemic control due to the avoidance of malabsorption[155].

The enhanced patient understanding of the consequences of total pancreatectomy, early education on diabetes (all patients should consult an endocrinologist immediately following their operation), advances in medical therapies, and blood glucose monitoring might all have contributed to enhanced glycaemic control[161].

Goal-directed fluid therapy

Early oral nutrition has to be associated to the individualised postoperative fluid therapy that is administered in accordance to the optimisation of stroke volume. Dynamic parameters such as stroke volume or pulse pressure variation can provide a more favourable prediction of fluid responsiveness. Oesophageal Doppler-guided fluid optimisation has been shown to improve patient outcomes, although this method cannot be performed on conscious patients[116,117]. Fluid challenges and the leg-raising test can represent simple and valid alternatives[118]. Thus, oral nutrition has clearly be associated with a progressive decrease of intravenous fluids.

Pain relief/non opioid oral analgesia

One aim of fast track surgery is to obtain favourable pain control, which is intended to enable patient mobilisation, coughing and early nutrition. One of the modern principles for analgesia is the concept of opioid-sparing, which enhances recovery by avoiding the opioid-related side effects. In major abdominal procedures, the administration of continuous thoracic epidural analgesia with local anaesthetics has been demonstrated to be the most efficient technique to obtain optimal analgesia, allowing for early mobilisation, reducing postoperative ileus and pulmonary morbidity[162], and therefore acting as an important component of multimodal recovery strategies[163,164]. A mid-thoracic epidural activated prior to the initiation of surgery also blocks stress hormone release[165] and attenuates postoperative insulin resistance[166,167].

Fast-track clinical pathways in the peri-operative care of patients undergoing pancreatic resection provide for a catheter placed in the midthoracic level at T8/9 to achieve both analgesic and sympathetic blocks[168].

Small doses of epidural opioids have been shown to act in synergy with epidural local anaesthetics in providing analgesia, allowing reduced dosages of both agents[169].

For break-through pain, non-steroidal anti-inflammatory drugs and bolus epidural bupivacaine should be administered whilst the epidural is running. Non-steroidal anti-inflammatory drugs should be administered just prior to the removal of the epidural and continued until and/or after discharge.

As the optimal duration of continuous postoperative mid-thoracic epidural analgesia has not been established

in well-designed randomised trials, we suggest that two-to-three days might be a sufficient period for pancreatic surgery.

Patient-controlled analgesia using intravenous opioids does not provide the same efficient analgesia and elicits less beneficial physiological effects on surgical stress responses compared to local epidural anaesthetic techniques. However, it is performed whenever contraindications prevent the execution of peridural analgesia.

Intensive postoperative ambulation and prevention of venous thromboembolism

Among the standardised clinical pathways, which represent the basis of the fast-track programme, early mobilisation is a cornerstone. It has been shown to play a major role in postoperative functional recovery. Improved early ambulation can elicit beneficial effects in the resolution of postoperative ileus and can reduce the risk of lower extremity deep venous thrombosis. Furthermore, mobilisation might reduce pulmonary complications[170]. The risk for VTE, which is particularly high in this patient population, must be managed from the beginning of the preoperative period and continue during the entire surgical operation until the postoperative period as a result of early mobilisation and proper pharmacological thromboprophylaxis. At our University Hospital, we generally mobilise patients out of their beds for more than one hour from POD 1 and progressively increase the hours of mobilisation from POD 2. Patients who had undergone major abdominal surgery for gastrointestinal malignancies should be considered for post-discharge VTE prophylaxis for up to 4 wk following surgery during the following situations: residual or metastatic disease, obesity or previous history of VTE.

Intensive respiratory rehabilitation

Pulmonary complications following pancreatic resection occur in approximately one quarter of all patients[171]. Many pathophysiological modifications that occur under anaesthesia and/or following surgery can interact with each other, resulting in respiratory complications.

Reduced lung inflation is one of the basic causes of postoperative pulmonary dysfunction[172].

After upper abdominal and thoracic surgery, postoperative diaphragmatic dysfunction[173], which is the most important determinant of respiratory complications and atelectasis, is commonly observed and is caused by the mechanical compression of alveoli and the resorption of alveolar gases, which are the factors most commonly implicated in respiratory complications[174].

In recent years, breathing (deep breathing and directed cough) and chest wall physiotherapy have been introduced into clinical practice to prevent pulmonary complications. Physiotherapy includes a variety of manual treatments (postural drainage, percussion, clapping, vibration, or shaking) as well as the use of mechanical breathing devices (incentive spirometry, blow bottles, intermittent positive pressure breathing, and continuous positive airway pressure).

A systematic review showed that postoperative non-invasive ventilation, specifically continuous positive airway pressure (CPAP), improves hypoxaemia and reduces both postoperative complications and the requirement for intubation in patients undergoing abdominal surgery[170]. Furthermore, there is no specific study focusing on the role of chest physiotherapy after pancreatic resection; it is nonetheless included in the care plan at our institution. Every patient who has undergone pancreatic surgery is instructed to use a blow bottle (5 min/h) and undergoes an individualised exercise schedule that is designed by physiotherapists. Further, certain short courses of non-invasive mechanical ventilation (CPAP) can be performed as needed.

Intensive postoperative management

Despite continuous improvements in operative technique and perioperative management, the increasing age of patients undergoing major abdominal surgery exposes patients to an increasing number of postoperative complications, leading to increased morbidity, mortality, length of hospital stay, and hospital costs. Although the concept of fast-track surgery has questioned the traditional use of intensive care units, there is increasing evidence indicating that access to ICUs results in a more favourable impact on the outcomes of major abdominal surgeries.

In the case of pancreaticoduodenectomy, even high-volume centres report a major postoperative complication rate of approximately 20%[175]. Because of these observations, patients who undergo pancreatic cancer surgeries might benefit from admission to the ICU.

An ideal ICU model should involve the cooperation of the intensivists who primarily care for the patients with the primary physician and surgeon[176].

Current general concepts of fast track surgery have been implemented in intensive care units. Early mobilisation, early enteral feeding, and restrictive perioperative fluid management are generally performed at the ICUs of our institution. In addition to these programmes, ICU stays can offer extended haemodynamic monitoring, which is useful in goal-directed fluid therapy, the possibility of invasive and non-invasive ventilation, the continuous application of intravenous drugs or subsequently required extracorporeal procedures.

In summary, most patients who undergo elective pancreatic surgery for cancer do not necessary require intensive care admission, whereas high-risk patients might benefit from postoperative care in the ICUs. We suggest that surgical intensive care units play a pivotal role in the perioperative care of patients undergoing major abdominal surgeries, and patients with co-morbidities or elderly patients should be scheduled for intensive care treatment[177,178].

CONCLUSION

In recent decades, diagnostic modalities and the surgical treatments of PC have significantly progressed, de-

spite the fact that overall prognosis has only marginally changed. The management of patients affected by PC is complex and requires expertise in many fields. Multidisciplinary teams are necessary to optimise and improve the overall care and outcomes of patients. Because more patients are referred to surgery at an advanced age, a coordinated effort between surgeon and anaesthetist in terms of risk assessment is necessary, particularly for borderline resectable or unresectable disease cases (to spare the risk and cost of surgery for patients who are affected by advance disease and whose life expectancy might be potentially shortened by an unuseful and dangerous surgical operation)[179]. More favourable outcomes are attained if PC patients are appropriately referred to tertiary centres for assessment by surgical, medical and radiation oncologists, gastroenterologists, anaesthetists and other dedicated health care providers. The anaesthetist plays a key role in the preoperative assessment, intraoperative management and during the postoperative period assessment. For this reason, close cooperation between surgeons and anaesthesiologists is crucial for ensuring the safe performance of major gastrointestinal surgery with acceptable morbidity and mortality rates.

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