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REVIEW

Anesthetic and perioperative management of intestinal and multivisceral allograft recipient in nontransplant surgery

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Summary

As the survival rate of the intestinal and multi-visceral transplant recipients continues to improve, an increasing number of these patients present for either elective or emergency surgery related or unrelated to transplantation. The aim of this review is to focus on clinical issues related to the anesthetic and perioperative management of the intestinal or multi-visceral transplant recipient for nontransplant surgery. Specific issues concerning perioperative assessment and medications, choice of anesthetic drugs and techniques, and postoperative care management are reviewed.

Introduction

In the United States, more than 28 000 patients received solid-organ transplants in 2006, of which 175 were isolated intestine and 113 were multi-visceral transplants (including an intestinal graft) [1]. More than half of the patients who underwent intestinal transplantation (ITx) were children [2–6]. ITx has evolved and is currently accepted as a therapeutic option for selected patients with intestinal failure who develop serious complications including thrombosis of major vascular accesses, or complications related to total parenteral nutrition (TPN) (e.g. cholestatic liver failure, and catheter-related sepsis), that might result in life-threatening conditions. Intestinal failure, defined as an inability of the intestine to maintain nutrition and/or positive fluid and electrolyte balance without parenteral support, develops secondary to either loss of absorptive surface or dysfunction of the native small intestine [3,6]. Mesenteric thrombosis, midgut volvulus, gastroschisis are among the most common causes of intestinal failure in adult and pediatric recipients (Table 1).

Four types of ITx are currently performed, which include: (i) isolated ITx, (ii) liver-intestine transplantation, (iii) combined liver, duodenum and pancreas ('organ cluster'), and (iv) multi-visceral transplantation

Table 1. Common original causes of intestinal failure in recipients of intestinal or multivisceral transplantation.

Adults	Children
Superior mesenteric artery or vein thrombosis	Gastroschisis
Crohn's disease	Midgut volvulus (malrotation)
Intestinal trauma	Necrotizing enterocolitis
Midgut volvulus	Chronic intestinal pseudo-obstruction
Intra-abdominal desmoid tumor	Intestinal atresia
Pseudo-obstruction	Hirschsprung's disease
Radiation enteritis	Microvillus inclusion disease
Massive resection secondary to tumor	Intestinal polyposis
Retransplant	Retransplant

Table 2. Several common reasons for which transplant recipients require anesthetic management.

(a) Diagnostic procedures or standard protocol biopsies for the surveillance of rejection
Ultrasound guided biopsy
Computed tomography or magnetic resonance imaging
Bronchoscopy (opportunistic infections of the lung)
Endoscopy (for biopsies, or therapy e.g. bleeding varices)
(b) Surgical intervention for complications of transplantation
Postoperative hemorrhage
Thrombosis of the graft
Upper gastrointestinal bleeding (secondary to peptic ulcer, gastritis, CMV gastroenteritis)
Colonic perforation
Leak from gastrointestinal anastomoses, proximal or distal (ITx)
Infections of the peritoneal cavity (bacterial, opportunistic)
Bleeding varices (liver transplantation)
Pneumatosis intestinalis (ITx)
Pseudoaneurysm
Arterio-venous fistulae
Incisional hernias
Bowel obstruction
Biliary tract complications: leaks, obstruction
(c) Surgical intervention unrelated to the transplantation (e.g. trauma, tumor resection, cardiovascular surgery, etc.)

(MVTx) (concurrent transplantation of the stomach, pancreato-duodenal complex, small bowel and colon, with or without the liver and kidney, with the need for abdominal wall transplant in some recipients) [5,7,8]. Short-term (1-year) survival for intestinal or multi-visceral transplant recipients approaches 90% and 50% respectively, thus an increasing number of patients may present for either elective or emergency surgery relevant or irrelevant to transplantation [5,8–11]. Organ transplant recipients may present with acute or chronic somatic and psychological symptoms. Chronic immunosuppression may also affect the quality of life after ITx [12–14]. In Table 2, several common reasons for which transplant recipients may require anesthesia are present.

Postoperative hemorrhage is usually an early surgical complication (e.g. bleeding from vascular anastomoses), which needs intervention. Arterial thrombosis of the graft is a severe and life-threatening complication that might result in a rapid clinical deterioration, and to necrosis of the supplied organ. Venous thrombosis and blood outflow interruption may also present with a clinical deterioration. Leak from gastrointestinal anastomosis as well as biliary complications usually require surgical reconstruction.

Pancreatitis following pancreatic transplantation is a common complication, and in a majority of the cases is self-limited. Because of ischemic preservation injury, peripancreatic fluid collections may occur, requiring operative drainage and debridement of necrotic tissue. Abdominal complications, ranging from gastritis to visceral perforation and death, are recognized as a common risk of intra-abdominal organ transplantation. Increased risk for the development of colorectal and anal malignancies has been reported in solid organ recipients [15]. In addition, it has to be taken into consideration that immunosuppressed patients do not present with the typical symptomatology of abdominal sepsis, and high suspicion is required for the diagnosis of abdominal complications requiring surgery.

Solid organ transplant recipients sustaining trauma should receive the same initial resuscitation as any other trauma victim. Patients should be thoroughly examined for graft dysfunction [16]. The main skeletal complications are (i) fragility fractures and osteoporosis, and (ii) avascular necrosis leading to subchondral fracture and secondary osteoarthritis [17,18]. Osteoporosis is common in up to half of transplant recipients, the pathogenesis of which includes immunosuppressive medication, bone disease preceding transplantation, nutritional and lifestyle factors and derangements of the parathyroid-calcium-vitamin D3 and the pituitary-gonadal axes [19].

Recipients with isolated small bowel or multi-visceral allografts usually require a high level of specific or multidisciplinary support. Occasionally, an emergency situation may be encountered where anesthesiologists and surgeons are required to manage transplant recipients in hospitals that are not involved in transplant procedures. In such conditions, general considerations related to any transplant recipient are side effects and management of immunosuppression including possible interactions with the anesthetic management, as well as issues concerning the preoperative assessment, intraoperative and postoperative management.

Table 3. Current immunossupressive drugs and approaches for intestinal or multivisceral transplantation.

(a) Induction immunosuppression
Basiliximab or Daclizumab
Alemtuzumab (Campath-1H)
Rapamycin
Antilymphocyte or Antithymocyte globulins
OKT3
Corticosteroid: Methylprednisolone
(b) Maintenance immunosuppression
Tacrolimus (or Cyclosporine in alternative to tacrolimus)
Mycophenolate Mofetil
Azathioprine
Rapamycin
Corticosteroid: Prednisone
(c) Anti-rejection immunosuppression
Basiliximab or Daclizumab
Alemtuzumab
Antilymphocyte or Antithymocyte globulins
OKT3
Corticosteroid: Methylprednisolone

Alemtuzumab (Campath-1H) = Monoclonal anti CD52 antiboby.
Basiliximab or Daclizumab = Interleukin-2 receptor antagonists.
OKT3 = Monoclonal antibodies directed against CD-3 antigen of the surface of human T-Lymphocytes.
Cyclosporine, Tacrolimus = Calcineurin inhibitors.
Rapamycin = Signal transduction blocker in T-lymphocytes.

The imunossupressive regimen and anesthesia

Current immunosuppressive approaches include pharmacological agents presented in Table 3. Different protocols have been suggested with different strategies in mind for ITx and MVTx, such as reducing the incidence of rejection or limiting the toxicity of the therapy as much as possible [20]. Although the first successful cases were reported in the cyclosporine era [21], tacrolimus is the drug that allowed development of a consistently successful intestinal transplant series and to date is the maintenance drug of choice [22]. Tacrolimus toxicity constitutes a problem in ITx and tacrolimus sparing strategies have been developed such as the co-administration of rapamycin or alemtuzumab [20,23]. Induction therapy is ubiquitously used with either IL-2 receptor antagonists (basiliximab and daclizumab) [24] or more recently alemtuzumab (Campath-1H), a monoclonal antibody targeting CD 52. The latter provokes a profound depletion of the lymphocytes and thus is thought to prevent an aggressive immune response leading to rejection and allows a more gradual engagement of the host immune system [2,5,22,23,25,26]. As an induction agent alemtuzumab resulted in significantly improved renal function and reduced opportunistic infections, decreasing the average dose of calcineurin inhibitors and virtually avoiding the use of steroids [23,27]. Methylprednisolone is coadministered except in alemtuzumab cases.

Toxicity of various immunosuppressive regimens have been extensively reviewed [11,20] and common side effects that may affect anesthetic and perioperative management are summarized in Table 4. Newer tolerogenic protocols are currently under development involving low dose induction agents including calcineurin inhibitors to avoid the development of infection, malignancies and direct drug toxicity [28–30].

Among the complications encountered in MVTx transplantation, nephrotoxicity is one of the most troubling [5]. Tacrolimus or cyclosporine, induce the production of thromboxane A2, and perhaps endothelin, and are thus responsible for hemodynamic disturbances of the renal microcirculation [31–33]. In therapeutic doses, cyclosporine or tacrolimus, may cause a dose related decrease in renal blood flow and glomerular filtration rate, because of renal vasoconstriction. Increased dosage of some immunosuppressive drugs can cause an increase in serum creatinine levels. Drugs that may cause renal dysfunction when administered with cyclosporine or tacrolimus are amphotericin, NSAIDs, ranitidine, cimetidine, co-trimoxazole, tobramycin, gentamycin, melphanan, and vancomycin.

Cyclosporine might interfere with the metabolism of other medications (digoxin, lovastatin, prednisolone, etc) with resultant toxicity [20]. Oral administration of rapamycin and cyclosporine differentially alter intestinal function in rabbits [34]. Although azathioprine is not currently used very often, might be an alternative. One of the major adverse events is myelosuppression. Subsequently a dose reduction should be considered when leukopenia or thrombocytopenia is present. Medications that could increase azathioprine-induced myelotoxicity include allopurinol, angiotensin-converting enzyme inhibitors, sulfasalazine, and 5-amino salicilate acid [22,23,25,35,36]. Hearing impairment after organ transplantation has also been reported. For a majority of the patients the onset is early and bilateral, suggesting a dose-dependent toxicity [37].

In addition to the side effects of immunosuppressive drugs presented in Table 4, marked Cushingoid features, pathological fractures, or growth retardation might occur in children after transplantation [38,39]. Hypertrophic obstructive cardiomyopathy associated with the use of tacrolimus is a rare complication of liver and ITx seen almost exclusively among pediatric recipients something that, probably, has to be investigated preoperatively [40,41].

Immunosuppressive medications should be frequently adjusted to adapt to the immune imbalance brought on by severe stress. This period of the instability of the immune system can result in acute infection, graft

Table 4. Some of the more common side effects associated with some immunosuppressive drugs that have a direct impact on anesthetic and perioperative management.

	ALG/ATG	Aza	CyA	MMF	OKT3	Rap	Ste	TAC	IL2RA	C1H
Blood										
Anemia	–	+	+	+	–	–	–	–	–	–
Thrombocytopenia	+	+	–	+	–	+	–	–	–	–
Leucopenia	+	+	–	+	+	+	–	–	–	–
Cardiovascular										
Atherosclerosis	–	–	+	–	–	–	+	+	–	–
Hypert/pulm edema	–	–	++	–	+	–	+	+	+	–
Endocrine										
Diabetes	–	–	+	–	–	–	++	++	+	–
Osteoporosis	–	–	–	–	–	–	++	–	–	–
Hyperlipidemia	–	–	++	–	–	++	–	+	–	–
Adrenal suppression	–	–	–	–	–	–	++	–	–	–
Obesity	–	–	–	–	–	–	++	–	–	–
Neurotoxicity										
Seizures	–	–	+	–	–	–	–	+	–	–
Headache	–	–	+	–	–	–	–	+	–	–
Psychiatric disturbances	–	–	–	–	–	–	+	–	–	–
Nephrotoxicity	–	–	+	–	–	–	–	++	–	–
Hepatotoxicity	–	+	++	–	–	–	–	–	–	–
Gastrointestinal toxicity	–	++	++	++	+	–	+	+	+	–
Infections	++	+	–	–	+	–	+	–	+	+
Others										
Anaphylactic reactions*	+	–	–	–	+	–	–	+†	++	–
CRS‡	+	–	–	–	+	–	–	–	–	+
Cataract formation	–	–	–	–	–	–	+	–	–	–
Electrolyte abnormalities	–	–	+	–	–	–	–	+	–	–

ALG, anti-lymphocyte globulin; ATG, anti-thymocyte globulin; Aza, azathioprine; CyA, cyclosporine A; MMF, mycophenolate mofetil; OKT3, monoclonal antibodies directed against CD-3 antigen of the surface of human T-lymphocytes; Ste, steroids; Tac, tacrolimus; IL2RA, interleuchin 2 receptor antagonists (Basiliximab or Daclizumab); C1H, alemtuzumab (Campath-1H).

*Fever, chills, hypotension, bronchospasm.

†Only when given intravenously.

‡CRS (cytokine release syndrome) which includes CV collapse, pulmonary edema, seizures and renal failure.

rejection, or both. Immunosuppressive therapy should be continued during the perioperative period and adjusted in the presence of hepatic or renal insufficiency. The blood levels of patients receiving cyclosporine or tacrolimus should be monitored daily during the perioperative period. Low hematocrit levels might adversely affect the tacrolimus concentrations [42]. Intake of oral cyclosporine dose <4 h preoperatively, has been associated with subtherapeutic levels [43]. To maintain therapeutic blood levels, it is important to administer oral cyclosporine or tacrolimus 4–7 h before surgery [43]. The dose of other immunosuppressive drugs should not be altered perioperatively unless the route of administration needs to be changed from oral to intravenous. The oral dose of prednisone is equal to the intravenous methylprednisolone dose. Oral and intravenous doses of azathioprine are approximately equivalent. However, the experience from the renal transplant population points out that a supplemental 'stress-coverage' steroid dosage is probably not necessary, except in transplant recipients recently withdrawn from this [44,45].

Interactions between immunosuppressive and anesthetic drugs

Only cyclosporine A interaction with anesthetics has been extensively studied. Information on newer drugs is limited. The major immunosuppressants are metabolized through the cytochrome CYP 3A system. Medications given during anesthesia or perioperatively may affect their blood levels. Rats or mice pretreated with cyclosporine A have prolonged sleeping times after administration of barbiturates [46–48]. A single IM dose of cyclosporine increased pentobarbital hypnosis and fentanyl analgesia in mice [47]. Conversely, pretreatment of cyclosporine provokes a dose dependent increase in the MAC of isoflurane [49]. Isoflurane anesthesia in rats may reduce gastric emptying and absorption from the

proximal small bowel and therefore alters the kinetics of oral cyclosporine [50]. Propofol infusion does not modify the cyclosporine blood levels in humans [51]. Cyclosporine may enhance the effects of muscle relaxants atracurium, vecuronium, and pancuronium. Therefore, transplant recipients receiving cyclosporine as immunosuppressive therapy may require a lower dose of nondepolarizing muscle relaxant, and the recovery time may be prolonged [52,53]. In patients with end stage renal disease undergoing kidney transplantation, the initial dose of neuromuscular blocking drugs should be increased in the presence of azathioprine (atracurium by 37%, vecuronium 20%, pancuronium 45%) [54]. Tacrolimus and rapamycin treatment of normal human skeletal muscle increased halothane induced contracture [55]. Tacrolimus, rapamycin, and cyclosporine A play a role in nerve regeneration/neuroprotection [56]. Markers of coagulation activity and fibrinolysis are increased by cyclosporine A and OKT3 perioperatively while OKT3 induced also an increase in endothelial TPA [57]. Azathioprine withdrawal in the perioperative period in patients taking warfarin may precipitate bleeding [58].

On the other hand, anesthetic drugs have been reported to affect cell-mediated immunity in the surgical stress response [59]. Volatile anesthetics appear to suppress effector functions of both the innate and adaptive immunity, assist tumor growth in animal models, and facilitate aggregation of certain neurodegenerative disease proteins. Local anesthetics block neurons, but are also potent anti-inflammatory drugs. Morphine has recognized immunosuppressive functions, which the newer, synthetic opioids do not seem to share [60].

Anesthesia in the perioperative period

Table 5 summarizes general principles common to all transplant recipients as well as certain specific considerations that can be applied to isolated intestinal or multivisceral transplant recipients who undergo anesthesia and surgery.

Table 5. General principles applied to any transplant recipients and certain specific considerations applied to isolated intestinal (ITx) or multivisceral transplant (MVTx) recipients who undergo anesthesia and surgery.

General principles	Specific considerations
Preoperative early communication with the transplant center, particularly regarding type of transplantation and immunosuppression regimens	Distinguish between isolated intestinal transplantation or multivisceral transplantation (patients in the latter group are generally more ill) Immnunosuppression is one of the most problematic issues in ITx due to the abundance of lymphatic tissue
Perioperative adjustment of immunosuppressive medications	Consider specific drug interactions between immunosuppressive drugs and anesthetics Toxicity of immunosuppressive drugs
Careful preoperative evaluation of: Graft's function Presence of rejection Presence of infection Function of other organs, particularly those that may be compromised due to either immunosuppressive drugs or dysfunction of the transplanted organ	Patients must undergo thorough physical examination searching for: Dehydration causing relative hypovolemia Chronic diarrhea Malnutrition Rejection in ITx is frequent and leads to bacterial translocation and sepsis
Preoperative medical optimization	May require ICU management if the patient is severely decompensated with electrolyte abnormalities, respiratory distress or hemodynamic instability
Perform aseptic techniques to minimize the risk of infection	Restoration of venous access might be particularly challenging in these patients due to vein thrombosis from long-term TPN
Ensure appropriate equipment required for safe anesthesia and monitoring	Proper anesthestic technique based on status of patient and type of surgery. Proper monitoring is necessary for fluid management. Maintain hematocrit levels 28–30%. Manage hypovolemia with volume reintegration associated with infusion of diuretics
Organization of the anesthetic techniques and agents, in a fashion that minimizes injury to the transplanted organ(s)	
Precise perioperative fluid management	
Organization of the patient's immediate postoperative care. Careful communication between the anesthesiologist and the physicians, nurses, respiratory therapists and dieticians who will be caring for the patient. Appropriate postoperative analgesia	Nutritional support is difficult in intestinal transplant recipients. Enteral nutrition should be initiated as soon as possible but often these patients need a highly individualized diet

Preoperative assessment of intestinal or multi-visceral transplant recipients

The primary objectives of preoperative evaluation of any transplant recipient are (i) to exclude conditions related to graft(s) malfunction, and thus evaluation of the transplanted organ(s) function, (ii) to determine functional adequacy of other organ systems. Conditions observed after ITx or MVTx that should be ruled out preoperatively include allograft rejection, infection of the transplanted organ(s), post-transplant lympho-proliferative disease and graft-versus-host disease.

Rejection

One of the most sobering issues in ITx and MVTx is the significant alloimmune response and subsequent rejection of the intestinal graft, an event that occurs more frequently and with greater severity than any other abdominal organ. The potential reasons include the heightened immunogenicity and significant donor lymphoid volume in the organ. There is evidence that patients who undergo surgery during a period of rejection have a higher morbidity [5,61,62]. Acute cellular rejection is now identifiable by bowel biopsy histology, and international pathology grading systems have emerged [63]. Improvements in endoscopic monitoring help establish potential sites of rejection. Serial endoscopies and graft biopsy are essential to diagnose rejection and avoid over-immunosuppression of the patient [64,65]. Acute vascular rejection as well as chronic rejection (chronic allograft enteropathy) are entities, which will probably be understood in detail in the future as patient survival improves. It is important to realize that rejection in these patients leads not only to loss of graft function but also to bacterial translocation and increased risk for systemic infection further augmented by the intense immunosuppressive regimen used.

Infection

It has been identified as the major cause of mortality and still remains as the most serious complication among intestinal transplant recipients. Because of immunosuppression, organ denervation and lymphatic dysfunction, which affect intestinal permeability and absorption in the post-transplant period, intestinal transplant recipients are prone to infection. Bacterial, viral, fungal, or protozoan infections predominate [66]. Ischemia, rejection, or enteritis are common reasons for damage in the intestinal mucosal barrier leading to bacterial translocation and subsequent sepsis in this transplant population [67]. Bacterial infections are very common and among the early complications after intestinal transplantation. Sepsis is one of the main causes of death. Approximately half of the postoperative bacteremias observed after isolated ITx or MVTx originate from central venous catheters. Abdominal (peritonitis, intra-abdominal collection, and abscess), wound infections or respiratory infections reflect the recipient's condition of chronic deterioration superimposed with the effects of a prolonged abdominal visceral surgery [68,69].

Post-tranplant lympho-proliferative disease

This is a proliferation of EBV-positive lymphoid cells that progresses from lymphoid hyperplasia to frankly malignant lymphoma [70,71]. It represents a serious complication of ITx, lethal in 1/3 of total morbid cases, and tends to occur at its highest incidence approximately 2 years post-transplantation. Reduction in immunosuppression is the first line of treatment for low grade post-transplant lympho-proliferative disease (PTLD) and rituximab therapy is very useful in the treatment of some forms of PTLD [72,73]. Handling the level of the immunosuppressive regime is a very delicate procedure as reducing the dose in the perioperative period may increase the risk of rejection.

Graft-versus-host disease

This occurs in approximately 5% of patients (7% in children) receiving ITx, which is 5–10 times higher than any other solid organ transplantation. It is because of the large number of lymphoid cells in the small bowel and is manifested with skin and gastrointestinal changes (rash, blisters, ulceration of oral mucosa, diarrhea), pancytopenia, pneumonitis, altered mental status or native liver dysfunction [74].

Clinical and laboratory evaluation

Preoperative evaluation and testing should be guided based on patients' history. Laboratory evaluation for any isolated intestinal or multivisceral transplant recipient should include complete blood count, assessment of metabolic, acid–base, fluid, electrolyte and coagulation status as well as standard liver and renal function tests.

The patient's medical, surgical and anesthetic history should be reviewed. Recipients of isolated ITx are generally less ill than those in whom multiple organs have been transplanted. Testing of the patient's cardiopulmonary status should include at least a 12-lead electrocardiogram, and chest radiography. A 2D echocardiogram is helpful to screen for gross abnormalities and if clinically indicated, pulmonary function studies and a dobutamine stress echocardiography should be considered [75]. Some multivisceral transplant recipients may present with a hypercoagulable state as well [76]. Patients who have received ITx for protein C, S, or antithrombin III deficiency are more likely to suffer from perioperative thrombotic events in

the perioperative period following nontransplant surgery [77].

Electrolyte imbalance may be because of diarrhea and dehydration from a short native or transplanted colon. Long-term total parental nutrition (TPN) or diarrhea, which may occur in the post-transplant period predispose [67]. Patients with isolated small bowel or multi-visceral allografts may present with profound secretory diarrhea in the absence of rejection or infection [62]. Severe metabolic acidosis is present, if a vascular complication of the graft exists (e.g. main artery thrombosis) or because of systematic consumption and loss of bases.

Disturbed liver function is common in recipients of combined liver-small bowel, cluster graft, or multi-visceral transplants. Patients with liver dysfunction (induced mainly by TPN) might recover without the need of a liver transplant, if the liver biopsy demonstrates reversible injury [62]. In the combined liver intestine recipient, the presence of jaundice, pruritus, alterations in the color of urine or stools, asterixis, ascites, or edema, unexplained fever or signs of late or chronic rejection (elevation of bilirubin, AST, ALT levels, loss of bile ducts) should be investigated. In these patients, the volume of distribution of drugs, metabolism and excretion is variable.

Renal dysfunction and decreased glomerular filtration rate as a result of hypovolemia, antibiotic therapy or immunosuppression during the early post-transplant period, might be observed in the isolated intestinal or multi-visceral transplant recipients. In patients with failed pancreatic grafts, the management of glucose levels and acid–base status should be the same as for any diabetic patient, and tight glycemic control in both diabetic and in nondiabetic hyperglycaemic patients' results in improved survival in surgical patients [78]. Pancreatic transplantation does not protect from diabetes-related cardiovascular disease and symptoms of autonomic neuropathy may improve but not always recede in the pancreas transplant recipient [79].

Anesthetic drugs and techniques

The anesthetic management of the intestinal or multi-visceral transplant recipient for nontransplant surgery depends on: (i) the length of time since the transplant procedure, (ii) the function of the graft, and (iii) the presence or absence of extra-intestinal organ dysfunction. For intra-abdominal surgery, the anesthesiologists should be aware of the possibility that a difficult surgical approach could occur. These patients may have undergone several laparotomies in the past, and therefore multiple adhesions may be present leading to surgical bleeding and the need for a large volume of blood transfusions and fluid resuscitation. The surgical procedure may be very long, especially if attempts are being made to ameliorate complications after transplantation, which may involve reconstruction of anastamoses and/or the use of vascular grafts [65]. Chronic treatment with TPN may develop chronic thrombosis at various access sites. Evaluation with venous doppler studies and venous angiography may be necessary to assess patency of central veins before surgery and minimize the risk for complications from multiple puncture sites [80,81]. Aseptic techniques should be performed to minimize the risk of infection in any immune-compromised patient [82,83].

General (balanced and total intravenous) and regional anesthesia have been successfully used for nontransplant surgery [11,84]. Most induction agents can be used. Propofol is a safe choice [85–87] but etomidate might be preferable in cardiovascularly unstable patients. In the presence of encephalopathy (e.g. liver transplant recipients requiring surgery in the early post-transplant period), benzodiazepines should be avoided and the use of high-dose opioids must be limited. Opioids such as fentanyl and morphine are reasonable options for intra- and postoperative analgesia. If the patient has some degree of renal dysfunction, the active metabolites of meperidine (normeperidine) can accumulate, as well as the active metabolites of morphine (morphine-6- and morphine-3-glucuronide), which may cause prolonged sedation postoperatively [88]. Short-acting opioids with extrahepatic metabolism, such as remifentanil, may be considered for intraoperative analgesia [89]. Isoflurane, sevoflurane, and desflurane in clinically administered doses, are appropriate volatile anesthetics [87,90–93]. Nitrous oxide must be avoided because of bowel distention. If hepatic or renal dysfunction exists, muscle relaxants, which are not metabolized by the liver and do not rely on renal excretion, such as atracurium and cisatracurium, are superior choices. Succinilcholine could be administered in the absence of hyperkaliemia but rocuronium or mivacurium are alternatives for rapid sequence induction [93]. If renal or liver function is impaired, choice and dosage of drugs given during the perioperative period should be adjusted accordingly [11,84].

Careful attention should be paid to transplant recipients receiving low-dose heparin, dextran, or anti-platelet agents for graft thromboprophylaxis in the early post-transplant period [94]. If an epidural or spinal technique is planned, clotting studies and platelet count should be within normal values. Bupivacaine or ropivacaine administration is safe in clinically relevant doses [95–97]. Adding an opioid to the local anesthetic extends the surgical anesthesia to different levels, hardly reached by the administration of the local anesthetic alone [98,99].

Perioperative medications

Inotropic and vasopressor drugs should be available, particularly in vasodilated septic patients [46]. Adequate maintenance of preload with crystalloids or colloids is important in any transplant recipient undergoing nontransplant surgery. Hypothermia should be prevented, particularly at the pediatric population [41,87]. Children scheduled for elective surgery should not fast for excessive periods preoperatively or allowed to become volume depleted [61]. Hyperkalemia and hypomagnesemia may be observed with cyclosporine or tacrolimus therapy [26,32,100,101] Therefore, monitoring of ionized magnesium levels or empiric replacement of serum magnesium (2–4 g) is recommended. Transfusion therapy with red blood cells should be aimed to maintain hematocrit levels of 28–30% [102]. Overtransfusion of blood products leading to hemoconcentration could be the cause of a graft's arterial thrombosis, a complication with high mortality rate in the transplant population [103]. Broad spectrum antibiotics for prophylaxis or for treatment of a suspected or confirmed infection should be continued during the time of operation [11,84,85]. Because of the possibility of endocrine secretory tumors such as carcinoids, octreotide should be available [104]. In patients with coronary artery disease, perioperative β-blockade is indicated [105].

Monitoring

The choice of the forms and extension of monitoring correlate with the patient's history, clinical condition, planned surgery and expected blood loss. For minor procedures, routine noninvasive monitoring (electrocardiography, pulse oximetry, end-tidal gas analysis, noninvasive arterial pressure measurement and temperature control) should be applied. Invasive cardiovascular monitoring should be considered if indicated and if appropriate vascular access is available to allow placement of a Swan-Ganz catheter. Trans-esophageal echocardiography (TEE), in patients requiring more advanced cardiac monitoring and scheduled for general anesthesia, is the first choice in patients with thrombosis of the upper circulation. It allows a noninvasive assessment of myocardial function and aids in the management of the patient's volume status (fluid volume and inotrope titration). Hence, TEE reduces the risk of catheter related sepsis, potentially a life-threatening complication in this patient population. Early diagnosis of thrombo-embolic events is another advantage of this technique [102].

Pulse contour analysis for measurement of cardiac output (PiCCO) is another less invasive modality than pulmonary arterial catheterization. This device enables also the assessment of intravascular blood volume and therefore guides correct intraoperative fluid management [106]. If postoperative monitoring of cardiovascular function is indicated, periodic bedside transthoracic echocardiography should be considered rather than more invasive techniques.

Coagulation monitoring is best provided by thromboelastogram (TEG) although platelet count, activated prothrombin time, thromboplastin time, fibrinogen, and fibrinogen decay products can also supply information and guide reintegration therapy [102].

Airway management

After small bowel transplantation, intestinal motility returns after 1–2 weeks, but gastric emptying may continue to be delayed for a longer period [107]. In addition, ascites or gastrointestinal complication(s) increase the possibility of regurgitation and rapid sequence induction with application of cricoid pressure may need to be performed. Severe perioperative airway obstruction may be caused by an underlying PTLD [5,84,108]. Diabetic stiff joint syndrome, which may affect the atlanto-occipital joint, could make direct visualization of the vocal cords difficult or impossible [109]. If the airway appears to be potentially difficult, awake fiberoptic intubation should be strongly considered. Oral endotracheal intubation is preferred over nasal intubation because of the potential of infection caused by nasal flora [110]. Because the seizure threshold of patients treated with cyclosporine or tacrolimus may be lowered, hyperventilation during mechanical ventilation should be avoided [35]. Ascites, intestinal edema, pleural effusions, or the existence of right hemidiaphragm dysfunction because of recent liver transplantation may compromise the respiratory function during the postoperative period after an intra-abdominal surgery. In addition, hypoproteinemia increases the risk for the development of ascites and pleural effusion [111]. Spontaneous ventilation is beneficial in the hemodynamically stable patient, promoting hepatic venous drainage and liver graft circulation [112]. Mobilization and physiotherapy, including pulmonary toilet are also useful.

Early extubation (<3 h postoperatively) can be attempted if hemodynamic stability, alveolar-arterial oxygen gradient <200 mmHg, no evidence of encephalopathy, and no severe electrolyte abnormalities coexist. Early extubation results in a shorter ICU and hospital stay, and reduces the costs and risks for postoperative respiratory infections. The use of short-acting anesthetic drugs, appropriate intraoperative extubation criteria, and good postoperative analgesia make early extubation possible and effective [113,114]. All transplant recipients do not routinely need admission to the ICU after surgery. ICU

admission should be considered in patients with severe or unstable coronary artery disease, ischemic cardiomyopathy, severe electrolyte abnormalities, respiratory dysfunction or hemodynamic instability.

Postoperative pain management

There are no enough data with regard to management of perioperative pain in the late post-transplant period for nontransplant surgery. Most patients are managed adequately with intravenous morphine administered by patient-controlled analgesia (PCA) and transitioned to oral opiates after a few days. PCA is safe and effective also for pediatric patients [87,115–117]. Oxycodone may be used in the absence of liver or renal dysfunction [118,119]. If long-term administration of opioids exists, the possibility of tolerance and dependence and the need for slow weaning from morphine should be considered.

Postoperative pain is lower in patients treated with local anesthetics and opioids administered epidurally than in patients treated with systemic administration of opioids [99,120]. Epidural block and wound infiltration are appropriate techniques for postoperative analgesia also in children [89]. Paravertebral blocks are gaining popularity for intra- and postoperative analgesia after upper abdominal surgery although experience in transplanted patients is limited [121,122].

The frequency and severity of complications (e.g. gastrointestinal hemorrhage, nephrotoxicity, hepatic dysfunction) induced by nonsteroidal anti-inflammatory drugs is a relative contraindication for their use [123,124]. Common analgesics, such as acetaminophen, can be used in the pediatric population, according to individual features of the child. There is no evidence of any increased risk associated with central blockade if the child is on long term steroids [125]. It is necessary to establish a global approach to pain management, including both psychological and medical issues. Postoperative acute pain management should also be coadiuvated by agents with anxiolytic and/or antidepressive activity and a_2-adrenergic agonists (clonidine or dexmetomidine) titrated accordingly to the desired clinical effect and the potential of side effects [120].

Nutrition

Preserving the trophism of the transplanted intestine is one of the main objectives of postoperative care and requires a continuous supply of nutrients [126]. The enteral feeds must be initiated as soon as intestinal function resumes and anastomotic integrity is established. TPN however should be continued if the patient does not satisfy the daily nutritional requirements [127]. Highly modified feeds are used after transplantation due to perioperative manipulation, procurement and the fear of induction of food allergies related to immunosuppression and should be continued until the patient can progress to a more age-appropriate formula [13]. If this individualized nutritional regimen is altered by the need for incidental surgery or by an intercurrent illness consultation with the transplant team and dietician should be sought for perioperative advice.

Conclusions

The increasing prevalence of previously transplanted patients makes it likely that every anesthesiologist will care for patients with end-organ failure or a transplanted organ, either for accidental or transplant-related surgery in the future. Appropriate knowledge of the physiology of the transplanted organ(s), the pharmacology of the immunosuppressive drugs, the presence of associated organ dysfunction(s), and the underlying conditions requiring surgery is essential for successful anesthesia and perioperative management of these patients independent of the type of surgical procedure. Additional research should be performed in order to identify perioperative issues and facilitate the formulation of guidelines for anesthesia in this particular transplanted population. A registry for the perioperative problems of patients with an intestinal or a multi-visceral allograft is needed in order to formulate appropriate management and follow up guidelines.

Authorship

GK, TS and NP wrote the paper. AP, PM and NA collected and analysed data. EAP, VS and AGT carried out the senior revision.

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