Oxford Textbook of Transplant Anaesthesia and Critical Care

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Publisher: Oxford University Press
Print ISBN-13: 9780199651429
DOI: 10.1093/med/9780199651429.001.0001

Print Publication Date: Oct 2015
Published online: Oct 2015

Anaesthesia for non-transplant surgery in the organ transplant recipient

Chapter:
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DOI: 10.1093/med/9780199651429.003.0039

Introduction

According to the OPTN, in the US over 59,000 patients received a transplanted organ in 2014 alone (OPTN, 2015). Post-transplant survival ranges between 60 and 90% at 5 years, with good functional outcome. In general, 50% of organ transplant recipients enjoy good quality of life and return to work. However, restoration of pretransplant functionality is highly dependent on the organ transplanted. For example, 61.5% of kidney transplant recipients, 57% of liver recipients, and 37% of lung transplant recipients experience full recovery (Paris et al., 1998). Irrespective of functionality, all transplant recipients require some form of immunosuppression. Immunosuppressive agents may cause side effects. Patients may experience episodes of infection, which may lead to changes in health status. In fact, post-transplant status can be considered a new chronic illness that can affect physiological function, requiringa

tailored anaesthetic management plan (Keegan and Plevak, 2004). Since the post-transplant period constitutes a new complex state, the transplant recipient deserves meticulous attention during preoperative preparation and during anaesthetic management for non-transplant surgery.

These patients may need re-operation for early or late complications of post-transplant surgery, or require elective diagnostic and surgical procedures, or suffer traumatic events or other emergencies (Karam et al., 2003). From the simplest procedures to the higher risk ones, the transplanted population can represent a challenge for the anaesthesia provider.

Perioperative management

In general, preoperative evaluation and screening of the transplant recipient for non-transplant surgery should be guided by the medical and surgical history of the organ transplanted, as well as the risks of the planned surgical procedure. Transplant recipients in most cases experience a protracted state of end-stage organ disease prior to transplantation. Depending on the duration and severity of end-stage illness, secondary organ function may be compromised, particularly cardiovascular (CAD) and pulmonary (i.e. portopulmonary hypertension) complications.Therefore meticulous cardiopulmonary screening is mandatory. A few patients will receive a transplant in the early stages of the disease, such as in the case of malignancies (i.e. hepatocellular carcinoma), and will present in relatively good health. But the majority will be transplanted in the late stages of end-stage organ disease, with multiple systems affected, and, in some instances, poor nutritional status. However, many of the non-functional and systemic organ-related complications are corrected with successful transplantation (Gohn and Warren, 2006).

A complete blood count (CBC) should be performed in every transplanted patient, as well as establishment of baseline coagulation status (PT-INR, PTT, and platelet count) prior to surgery. *Anaemia* is a common denominator in solid organ transplant recipients and is multifactorial, commonly associated with a variety of related chronic conditions, such as poor nutrition, kidney dysfunction and failure, haemodilution, hypersplenism, and the side effects of immunosuppressive or anti-infective medications, among other non-specific causes. In a recent study, upwards of 30% of transplant recipients were found to have haemoglobin concentrations below 12 g/dL (Malyszko et al., 2012). *Thrombocytopaenia* secondary to hypersplenism is another common finding among patients with cirrhosis and ESLD in liver transplantation. It may also result from immunosuppressors (Gohn, 2006). It is important to note that transplanted patients as a group experience some degree of *renal insufficiency*. The incidence of renal insufficiency varies with the organ transplanted but is estimated at 18% of liver recipients, 32% of heart recipients, and 20% of lung recipients (Ojo et al., 2003). Approximately

29% of patients on long-term CNI therapy will eventually progress to ESRD and require RRT.

Metabolic assessment is important in the preoperative evaluation of the transplant recipient, especially electrolytes (serum Na^+, Ca^{2+}, K^+, and Mg^{2+}), acid-base status, and serum BUN and Cr levels. Patients receiving RRT should be dialysed as close to the day of surgery as possible, to correct these values. Intestinal transplant recipients with or without indwelling catheters for supplemental TPN can be suffering from *diarrhoea* or *dehydration* and *hypercoagulation* or *thrombosis*. Diarrhoea and dehydration can result in electrolyte imbalances, as well as acid-base disturbances (Kostopanagiotou et al., 2008). Thrombosis can create vascular access problems. Metabolic alterations may be chronic or reflect an acute underlying condition, such as infection with or without septicaemia or graft thrombosis. In the liver transplant recipient, standard LFTs should be evaluated (AST, ALT, bilirubin, and PT/PTT).

Transplanted patients receive routine immunosuppressive medications that may aggravate risk factors for CAD, such as *hypertension*, *hyperlipidaemia* and *diabetes*. As a result, CAD is highly prevalent and multifactorial in the transplant population and it is not reversible after transplantation. For this reason, careful cardiovascular evaluation and screening is paramount. Among kidney transplant recipients younger than 45 years of age, perioperative cardiovascular mortality is almost ten-fold higher than in older surgical patients (Foley et al., 1998). A review of cardiovascular indices within 30 days of surgery should be done. If more recent evaluation is warranted, this should be dictated by the patient's clinical status and the procedure to be undertaken. *Hyperglycaemia* requiring perioperative management for glycaemic control in any transplanted patient, including patients with a failed pancreatic graft, will be the same as in any diabetic patient. Hyperglycaemia in the setting of high-dose steroid immunosuppression is a common finding among transplanted patients. Tight glycaemic control in the perioperative period results in improved survival in surgical patients (Coursin et al., 2004).

Immunosuppression

Immunosuppression is the common denominator in every transplanted patient. There is a delicate balance between organ acceptance, risk of rejection, and infection, on the one side, and risk of adverse effects and dose of immunosuppression, on the other. Immunosuppressive protocols (type and dose) will vary from centre to centre and depend on the graft, but usually consist of a cocktail of different agents (see Chapter 11). Plasma drug levels are monitored closely for prevention of side effects and fine-tuned to avoid rejection. 'Fine-tuning' of plasma levels is an art that determines the long-term success of organ transplantation. Other drugs that form part of the post-transplant drug regimen may include antibiotics, and antifungal and

antiviral therapy, which will need to be verified and continued according to schedule by the anaesthesiologist in the perioperative period.

Immunosuppressive therapy should be continued during the perioperative period and the dose adjusted in the presence of hepatic or renal insufficiency. The stress of surgery may affect absorption and metabolism of these drugs, thereby altering plasma levels. It is extremely important for the surgical team to communicate to the anaesthesiologist the drug regimen and the doses of drug(s) utilized. It is also essential for the transplant anaesthesiologist to have an understanding of the actions, interactions, and potential side effects of immunosuppressive drugs.

There are insufficient data on anaesthesia and immunosuppressive drug interactions. Information on newer agents is limited and most available data deal with the use of cyclosporine A, which is no longer first-line therapy for immunosuppression. In the section 'Corticosteroids' we will present a brief synopsis of the most commonly used agents and implications for anaesthetic management.

Corticosteroids

Corticosteroids are commonly used as adjuncts for induction and maintenance of immunosuppression and/or the management of acute or chronic rejection. These drugs cause immunosuppression mainly by sequestration of CD4+ T-lymphocytes of the reticuloendothelial system and by inhibiting the transcription of cytokines (Thomanson, 1999). Adverse effects of corticosteroids are well recognized as they impact virtually every organ system in the body, producing many dose-limiting side effects, such as hypertension, diabetes, obesity, and osteoporosis.

The decision to administer steroid stress-dose supplementation in the transplant recipient remains controversial. These patients will have a degree of hypothalamic–pituitary–adrenal suppression; hence the need for supplementation has not been well established. Several studies have suggested that there is no clear indication for stress doses of steroids in transplant recipients who present for minor risk procedures (Thomason et al., 1999). The recommendation is to continue maintenance doses up to the day of the surgery without supplementation (Mathis et al., 2004). In the case of a major surgical procedure, however, supplementation is advised. The usual stress dosage has been 100 mg of hydrocortisone every 8 hours. This dose, however, is far higher than the physiological cortisol response, which peaks at 150 mg/day after major surgery and returns quickly to baseline. A review of this topic recommends administration of the usual dose preoperatively, plus 50 mg of hydrocortisone every 8 hours for 48–72 hours, and then quickly return the dosage to baseline after surgery (Brown and Buie, 2001).This strategy is designed to mimic the physiological response of the normal adrenal gland to surgical stress (Axelrod, 2003).

Calcineurin inhibitors

CNIs include cyclosporine and tacrolimus. They function by binding to calcineurin and preventing its translocation into the nucleus, thus affecting transcription and subsequent secretion of interleukin 2 (IL-2) by the T lymphocyte cell. Therapeutic drug monitoring is necessary to maintain adequate immunosuppression, but both drugs have a narrow therapeutic index, producing varying degrees of nephrotoxicity, neurotoxicity, and glucose intolerance. Their metabolism is dependent on cytochrome P450, and drugs that cause induction of P450 enzymes can affect plasma levels of these immunosuppressives. Examples of such drugs are amphotericin, non-steroidal anti-inflammatory drugs, ranitidine, cimetidine, co-trimoxazole, tobramycin, gentamicin, melphanan, and vancomycin. Cyclosporine may interfere with the metabolism of other medications (digoxin, lovastatin, and prednisolone), with resultant toxicity (Hirose and Vincenti, 2006).

To maintain therapeutic blood levels, it is important to administer oral cyclosporine or tacrolimus 4–7 hours before surgery (Brown et al., 1989). There have been reports of an increase in the MAC of isoflurane in rats pretreated with cyclosporine A, and delayed emergence when co-administered with barbiturates. This is most likely associated with metabolic CYP3 system interference. It is debatable whether this effect is relevant in clinical practice. Caution must be taken with the non-depolarizing neuromuscular blocking agents in patients receiving this class of immunosuppressives, since prolonged muscle relaxation and longer reversal times have been reported, and recommendations are to reduce neuromuscular relaxant dose (Gramstad et al., 1986).

Antiproliferative agents

Azathioprine and mycophenolate are antimetabolites that inhibit the de-novo and salvage pathways of purine synthesis. This results in lymphocyte T and B suppression, but also toxicity to bone marrow, the gastrointestinal tract, and the liver. Previously, azathioprine was the drug of choice, but its use has been supplanted by mycophenolate, which is available in two forms: mycophenolate mofetil (CellCept, Roche) and enteric-coated mycophenolate sodium (Myfortic, Novartis). The enteric-coated form has better gastrointestinal tolerability and bioavailability, but both have similar haematological (anaemia, thrombocytopaenia, and leucopaenia) and neurological toxicity profiles. No major anaesthetic drug interactions have been described for these agents (Zolezzi, 2005).

mTORinhibitors

Sirolimus (rapamycin) and everolimus inhibit large molecule kinase activity, termed the mTOR, thus causing arrest of the lymphocyte cell cycle. They are used concomitantly with CNIs in situations where there may be an increased risk for renal insufficiency (Murgia et al., 1996). Their use is associated with poor wound healing, and as such it is

advisable not to initiate therapy until 6 weeks after transplantation or other surgical procedures. A complication described with these agents is pulmonary toxicity, presenting as interstitial pneumonitis, with fever, haemoptysis, and diffuse alveolar infiltrate in the absence of infection. This idiosyncratic toxicity frequently presents during the first 6 months of therapy, and usually patients respond well with drug discontinuation, with resolution of symptoms within 3 months (Augustine et al., 2007).

Antibodies

This group of agents includes polyclonal and monoclonal antibodies. Even though some of these agents have been around for more than 30 years, the newest agents are the closest to the ideal immunosuppressant, exhibiting the lowest toxicity, specific activity, and prolonged effect.

OKT3

OKT3 is a murine monoclonal antibody directed against the CD3 component of the T-cell receptor, preventing T lymphocyte function (Berge et al., 1999). Acute administration of OKT3 causes cytokine release syndrome, which can include fevers, rigors, headache, dyspnoea, gastrointestinal side effects, and even life-threatening pulmonary oedema. Even though this syndrome has been described to occur within an hour of the first dose, close monitoring and premedication with tylenol, antihistaminic, and corticosteroid is required to prevent it. This syndrome improves with subsequent doses (Thillainathan et al., 2011).

Thymoglobulin

Thymoglobulin is a rabbit-derived polyclonal antithymocyte antibody. It is used as an induction agent and also as treatment of rejection in courses of up to 14 days. Thymoglobulin produces lymphocyte depletion, and can cause a milder form of cytokine release syndrome than OKT3 when administered. Therefore pretreatment with tylenol, antihistaminic, and steroid is recommended. Thrombocytopaenia and leucopaenia are common side effects and serum sickness has also been reported with its use (Lundquist et al., 2007).

Anti-interleukin-2 receptor monoclonal antibodies

Basiliximab and daclizumab block IL-2-mediated T-cell activation. The use of these antibodies is remarkable for its lack of toxicity when compared to monoclonal and polyclonal antibodies. Gastrointestinal upset and a case report of non-cardiogenic pulmonary oedema in young patients have been described (Bamgbola et al., 2003).

Alemtuzumab

Alemtuzumab (Campath-1H) is a humanized monoclonal antibody to the CD52 molecule that is expressed in lymphocytes (T greater than B cells)

and results in its depletion both centrally and peripherally. It is widely used in haematological malignancies (Morgan et al., 2012).

Common transplant-related complications

Transplant recipients, as a group, are at long-term risk of infection and rejection. It is important to be aware that these complications may arise at any time post-transplant.

Rejection

Rejection is a worrisome condition in transplant recipients for obvious reasons, and expert evaluation is advised when detected. Transplanted organ function usually recovers almost fully after transplantation, and early organ dysfunction is an ominous sign. The signs and symptoms of chronic rejection and infection are similar and may be concurrent.

In heart transplant patients, a decrease of voltage on the ECG, presence of arrhythmias, especially of atrial origin, decreases in functional status, and dyspnoea can all be signs of rejection (Blasco et al., 2009). Lung transplant recipients may present acutely with fatigue, dyspnoea, oxygen desaturation on exertion or at rest,and abnormal pulmonary function tests. The presence of fever and signs of obliterative bronchiolitis are indicative of chronic rejection in this population (Feltracco et al., 2011).

Liver transplant recipients can present with a wide range of signs, including malaise, fever, and elevated serum bilirubin and/or other LFTs (Zeyneloglu et al., 2007). In the renal transplant recipient, increasing serum creatinine, hypertension, oliguria, and proteinuria should alert the anaesthesiologist to kidney graft dysfunction (Rao, 1998).

Graft dysfunction among recipients of intestinal transplant may present with enteritis and malabsorption syndrome. In these patients these findings are of special concern since this condition weakens the mucosal barrier of the intestinal allograft, allowing bacterial translocation and risk of septicaemia. Evaluation of the stoma and enteroscopy with biopsy are indicated if rejection is suspected, and any elective surgical procedure under these circumstances should be reconsidered (Ruiz et al., 2007).

The anaesthesiologist should be aware of graft organ dysfunction, since it may have a major impact on functional reserve. More importantly, anaesthetic drug pharmokinetics and pharmacodynamics may be altered. In general, patients with marginal graft function are best managed in a centre with experience in caring for patients with transplanted organs, particularly when major surgical procedures such as cardiovascular surgery are contemplated.

Infections

Immunosuppression induces host tolerance of the new graft, but at the same time it makes the patient prone to infections. Over 80% of

transplant recipients are expected to have at least one episode of infection after transplantation. Infection is associated with high mortality among transplant recipients. These patients are at risk of opportunistic infections related to viral, protozoan, or fungal pathogens. Among the most common infections are *Candida*, *Aspergillus*, and*Cytomegalovirus* (Loinaz et al., 2003).

Immunosuppressive medications such as steroids and azathioprine will render the white blood cell count unreliable. These patients may not present with the typical signs and symptoms of sepsis or may progress rapidly to severe sepsis. Early diagnosis and initiation of empiric treatment is mandatory.

Neurological complications

Neurological complications should be of special concern to the anaesthesiologist. These may range from seizures and peripheral neuropathy, to brain infarcts and haemorrhages, and occur in up to 30–60% of transplant recipients (Patchell, 1994). The transplant recipient is more susceptible to neurological complications as a consequence of the combination of immunosuppressive regimens and shifts in electrolytes and fluids. Hypomagnesaemia causes aphasia and seizures. Central pontine myelinolysis (CPM) has an incidence of up to 17% after liver transplantation, based on autopsy results, and is associated with a high mortality rate of 50% or higher (Holmdahl et al., 2000). It has been associated with rapid correction of hyponatraemia, hypomagnesaemia, and other electrolytes, as well as the use of cyclosporine and tacrolimus (Fukazawa et al., 2011).

Post-transplant malignancies

Malignancies have a higher incidence in transplanted recipients. Epithelial malignancies, including those affecting the colon, skin, vulva, bladder, lung, and testes, are not uncommon and behave more aggressively than those in the general population. PTLDcan present within 2 years after transplant and carries a high morbidity and mortality. This entity is associated with the EBV, causing proliferation in lymphoid tissue with progression to aggressive lymphoma. The treatment includes expert management of immunosuppression (Abu-Elmagd et al., 2004).

This population of patients is at risk for GVHD and cardiac allograft vasculopathy, among other complications.

Perioperative management

Preoperative evaluation

The type of surgical procedure to be undertaken dictates to a large degree the anaesthetic plan for intraoperative care, monitoring, and postoperative management. Early in the post-transplant period, anaesthetic management may encompass a continuation of perioperative

transplant management. Early returns to the operating room for acute surgical complications such as bleeding require attention to resuscitation, haemodynamic stability, correction of coagulopathy, and correction of acid-base disturbances, as well as protection of transplanted organ function. Thrombosis of the graft may result in severe and rapid clinical deterioration with irreversible graft failure.

In the case of multivisceral transplantation a gastrointestinal anastomotic leak may require early reintervention. Months to years after transplant patients can present for elective procedures, diagnostic imaging, laparoscopy, abdominal incisional hernia, Nissen fundoplication for GORD, incision and drainage of abscesses, and caesarean section for childbirth, among others (Johnston and Katz, 1994). Orthopaedic procedures are common, since the transplanted patients may suffer from osteoporosis and bone fragility (Aaron and Ciombor, 2006).

Irrespective of the reason for surgery, if it involves areas of previous surgeries the anaesthesiologist should be prepared for a difficult surgical approach and the possibility of bleeding, requiring large volumes of blood. Trauma in a transplant recipient should be managed initially with the same resuscitation goals as in any other patient, but consideration and evaluation by a transplant team whenever possible is mandatory (Barone et al., 1997; Goffin and Devogelaer, 2005). Long hours of surgery with graft reconstructions may require postoperative critical care.

Intraoperative management

General anaesthesia

General anaesthesia is administered in the majority of organ transplant recipients who are scheduled for non-transplant surgery. The type of surgical procedure planned, whether or not the operation is elective or emergent, and airway assessment will dictate airway management, as usual. The anaesthesiologist should be aware of special considerations. For example, rapid sequence induction should be considered in patients with ascites and in intestinal transplant recipients, since gastric emptying is delayed for a prolonged period after transplantation (Mousa et al., 1998). Large lymphomas obstructing the airway have been described in the transplanted patient with PTLD (Hammer et al., 1998). In these cases, awake fibreoptic intubation may be required. There are no data on specific agents or combinations of agents as the best choice in transplanted patients. All anaesthetic agents and techniques have been safely used in this patient population (Cheng and Ong, 1993). Etomidate is still the drug of choice in patients with cardiovascular instability. Propofol is the most popular induction agent and its use has been described in euvolaemic heart transplant patients without complication, as well as in patients with uraemic kidney failure (Kirvela et al., 1992).

The requirement for neuromuscular blockade may be altered as mentioned earlier by immunosuppressive medications. Succinyl choline

can be used as usual in rapid sequence induction in the absence of hyperkalaemia and kidney dysfunction; rocuronium and mivacurium are other options. Atracurium and cisatracurium undergo plasma Hoffman elimination and they seem ideal for most procedures (Smith and Hunter, 1995). Vecuronium use is discouraged in liver-transplanted patients due to its reliance on hepatic metabolism and accumulation in patients with kidney dysfunction. In fact, studies have been done in the liver transplant recipient to predict quality of liver graft function based on the duration of vecuronium neuromuscular block (Lukin et al., 1995).

The inhalational agents sevoflurane, isoflurane, and desflurane have all been used in transplanted patients without complications. Isoflurane seems to be the preferred inhalational agent, especially in liver transplant patients, because it undergoes minimal biotransformation, with only 0.17% of the isoflurane taken up recovered in the form of urinary metabolites; it also has a safe haemodynamic profile, and organ-protective characteristics have been described.

The combination of intraoperative opioid analgesics is the practice of choice, and there are no major contraindications for their use. Caution is advised, however, in transplant recipients with renal dysfunction, since accumulation of active metabolites of morphine can cause prolonged sedation (Hanna et al., 1993). The use of short-acting opioids like remifentanil that undergo Hoffman metabolism has been recommended in abdominal surgery and is accepted practice in some centres, allowing for easier titration and early extubation. However, short-acting opioids present the disadvantage of poor postoperative pain control, in which case multimodal analgesia may be considered (Park et al., 2000).

Regional anaesthesia

Some transplant recipients will require long-term anticoagulation as a consequence of an underlying hypercoagulable state, and some others will be clinically hypocoagulopathic. Either way, careful assessment of coagulation is necessary prior to the use of regional blockade. Regional anaesthesia may be preferred when possible in the lung transplant recipient to avoid airway manipulation. Conversely, central neuraxial blockade in heart transplant patients (where the denervated heart is dependent upon preload for cardiac output) may cause haemodynamic instability due to sudden sympathetic blockade and loss of cardiac filling (Grimsehl and Levack, 2002). In this case, continuous epidural anaesthesia is preferred to spinal anaesthesia, and the safe use of bupivacaine or ropivacaine has been described (Riley, 1995). Lidocaine should be used with caution because of its negative inotropic actions, and adrenaline should be avoided in the heart transplant recipient.

Monitoring

Standard monitoring is recommended in every case, to include ECG, pulse oximetry, non-invasive blood pressure, end-tidal CO_2, anaesthesia gas analysis, and temperature control. The type, duration, and potential

for bleeding associated with the planned surgical procedure, together with an assessment of the patient's baseline preoperative cardiovascular stat, will determine the type of advanced monitoring modalities to be employed.

When large volume shifts or prolonged procedures are anticipated or the patient's underlying metabolic condition dictates frequent serum glucose, acid-base, and electrolyte monitoring, large-bore peripheral intravenous lines and/or invasive monitoring may be indicated. Whenever possible, ultrasound imaging for placement of central venous catheters and non-invasive haemodynamic monitors is recommended, for two main reasons: (1) the majority of these patients have had prior indwelling central venous catheters and this may create unexpected challenges to safe placement; and (2) these are immune-compromised patients with increased risk of catheter-related sepsis. TOE use in the transplant field has increased in recent years and is the routine monitor for high-risk procedures performed on kidney, liver, lung, and heart transplant recipients. The routine use of TOE is primarily governed by expertise and availability, as well as clinical indication. Other forms of non-invasive cardiac output monitoring, such as by pulse contour analysis, and indications for their use are discussed elsewhere in this book (Section 9). In our institution TOE is used instead of PA catheterization for haemodynamic monitoring (Cowie, 2011), when indicated. Needless to say, strict asepsis is essential when establishing venous and arterial access in these immune-compromised patients (Slota et al., 2001).

Antibiotic-impregnated catheters are routinely used in the transplant population in some centres; their use has proven to reduce colonization and associated infections in up to 60% of cases. Their use has been advocated when planning to use lines for a period in excess of 2 weeks (George et al., 1997).

Haemodynamic control

Haemodynamic stability is the main objective in the transplanted patient during high-risk procedures. Adequate volume status and monitoring is the basis of good haemodynamic control, and the maintenance of preload results in better perfusion in most uncomplicated cases (Della Rocca et al., 2002, 2009).

Electrolytes

Immunosuppressive therapy is associated with electrolyte imbalance. Therefore anaesthesia and surgery may aggravate electrolyte disequilibrium (Adu et al., 1983).

Careful intraoperative management of electrolytes is very important, especially potassium and magnesium; these are of special importance in the transplanted heart patient with conduction abnormalities. Since total body magnesium is difficult to measure and ionized magnesium is not always available, empiric magnesium supplementation may be necessary

in the transplanted patient (June et al., 1985). It is important to remember that severe electrolyte shifts can worsen neurological complications for which some of these patients are already at higher risk.

Glycaemic Control

There is controversy regarding intraoperative glycaemic targets and these apply to the transplant recipient as well. Pancreas transplant recipients should experience restoration of normal glucose metabolism unless there is graft dysfunction (Rickels, 2012).

Diabetic patients should be managed as any other diabetic patient. Post-transplant diabetes develops in 4–20% of patients. Careful glycaemic monitoring is recommended in all transplant recipients undergoing surgical procedures, since perioperative hyperglycaemia is associated with electrolyte imbalance, impaired wound healing, and a higher incidence of nosocomial infections.

Tight glycaemic control targets (80–110 mg/dL) are associated with hypoglycaemia; a recent review suggests a wider range of glucose maintenance below 150 and avoidance of hyperglycaemia (Russo, 2012).

Special considerations in the kidney transplant recipient

The kidney transplant recipient is the most commonly encountered transplanted patient undergoing non-transplant surgery. It is important to note that it is a misconception to believe kidney function is completely restored after kidney transplantation. In fact, kidney transplant recipients have a lower GFR than normal individuals, and despite a near-normal Cr value, perioperative management should incorporate a renal-protective approach. These patients will present with multiple comorbidities, such as hyperlipidaemia, hypertension, diabetes, and CAD. CAD is the leading cause of death among kidney transplant recipients during the first year after transplantation. Therefore the preoperative evaluation should focus on blood pressure and glycaemic control, optimization of electrolytes and acid-base status, as well as careful screening of cardiovascular function, preferably with 2-D ECG and/or stress testing (Lindholm et al., 1995).

Kidney allograft function is assessed with urine analysis, and serum BUN and Cr levels. Elevated BUN or Cr may indicate dysfunction due to graft rejection. The type of surgical procedure and the patient's medical condition will dictate the selection of anaesthetic technique. Regional anaesthesia, including central neuraxial blocks, can be performed in patients with normal coagulation status.

The anaesthetic plan should be established with the understanding that drugs that rely heavily on renal excretion for clearance will result in prolonged effects. Most induction agents have been used successfully, but caution must be taken with the use of ketamine in the hypertensive patient. Succinylcholineis contraindicated when potassium levels are

elevated. Inhaled agents such as isoflurane, desflurane, and sevoflurane have been used without complications.

The newly transplanted and functional kidney is able to clear neuromuscular blocking and anticholinesterase agents at the same rate as normal kidneys. However, whenever there is clinically detectable renal dysfunction the use of drugs not excreted by the kidney is advised (Kostopanagiotou et al., 1999).

Opiates for pain management area concern, since these patients will have the tendency to accumulate active metabolites, especially patients with graft dysfunction. Fentanyl is a good choice because it is well tolerated and lacks active metabolites (Sear, 1995). Non-steroidal anti-inflammatory medications should be avoided or used with caution.

The kidney graft may have suboptimal autoregulation of renal blood flow, making it susceptible to sudden blood pressure variations. Studies have demonstrated that adequate hydration during kidney transplantation results in less incidence of perioperative acute tubular necrosis (Carlier et al., 1982); this depends on the patient's underlying status. In general, volume should be optimized prior to the institution of diuretics to maintain urine output.

Anaesthetic considerations in the liver and multivisceral transplant recipient

Liver transplantation is the definitive treatment for patients with cirrhosis/ESLD. The procedure has an average survival rate of 90% at 1 year. The number of liver transplant recipients requiring non-transplant surgery is on the rise, and perioperative outcome is in part dependent on time since transplant, as well as the adequacy of liver graft function at the time of surgery.

In the post-liver transplant period, any necessary follow-on surgery usually is aimed at the correction of early liver transplant-related complications, such as bleeding and bile duct anastomotic leaks. It is prudent for the transplant anaesthesiologist to manage these patients during these early surgical complications, since expert management of coagulopathy and haemodynamics is usually warranted. Moreover, extrahepatic complications of ESLD, such as severe portopulmonary hypertension, or hypoxaemia from pleural effusions, hydrothorax, HPS, or persistent ascites may not be completely resolved within the first two postoperative weeks. In patients with delayed graft function, continuation of mechanical ventilatory support with supplemental oxygen may be required to maintain adequate oxygenation. Invasive haemodynamic monitoring may also be necessary to monitor and treat pulmonary hypertension (Kato et al., 2006). Furthermore, the hyperdynamic circulation typical of the patient with ESLD reverses itself slowly after liver transplantation (Eriksson et al., 1990).

In the first few weeks after liver transplant a variety of late complications may require surgical re-exploration. These include hepatic artery thrombosis or stenosis, portal or hepatic vein thrombosis, biliary anastomotic leaks, and/or biliary tract reconstruction (Faenza et al., 2006). In these cases, general anaesthesia is indicated.

LFTs usually return to normal within 2 weeks after transplant, although some degree of elevation in AST can remain for years afterwards, as a result of immunosuppression. Persistently elevated LFTs, total bilirubin, or INR PT/PTT may be indicative of delayed function or acute rejection. Chronic rejection will also lead to a rise in liver function indices.

In the months and years after liver or multivisceral transplantation, indications for surgery will vary. Regional anaesthesia can be considered on a case-by-case manner in the absence of coagulopathy.

If the surgical plan includes an abdominal approach, difficult dissection is expected, and the anaesthesiologist should be prepared with available blood products and resuscitation fluids. Most general procedures will not require massive transfusion. There is debate regarding absolute haemoglobin or haematocrit value as a target for transfusion therapy. It is important to understand that overtransfusion and haemo-concentration can lead to graft thrombosis (Tisone et al., 1988). Because of the high prevalence of renal dysfunction in these patients, fluid status and electrolyte balance should be carefully monitored. Depending on fluid shifts and electrolyte disturbances and the severity of renal dysfunction, haemodialysis may be needed perioperatively (Gines et al., 2003). Increase in splanchnic vascular resistance, which may occur when there is such high airway pressure, hypoxia, hypercapnia, coughing and bucking, or volume overload, will decrease the perfusion of the graft and should be treated promptlyor avoided altogether (Kostopanagiotou, 1999).

Since hepatic metabolic capacity for drug metabolism is restored early after reperfusion of the graft, most induction agents have been used successfully, but the net effect and duration of action of any drug is unpredictable. It is advisable to titrate to effect and select drugs with extrahepatic metabolism, particularly muscle relaxants. Isoflurane is the inhaled agent of choice for this population. Pain management with opioids is still the best option, although even with a functional graft some patients still require low opioid doses for pain management; patient-controlled analgesia can be a good choice in this population (Eisenach, 1989).

Anaesthetic considerations in the heart transplant recipient

The heart transplant recipient has a denervated heart. The donor graft has no parasympathetic, sympathetic, or sensory innervation. Therefore reflex sympathetic activity is absent. Beta-receptor density increases and

myocyte sensitivity to circulating catecholamines is enhanced, with intrinsic myocardial contractility remaining unaffected (Blasco, 2009). Since heart-transplanted patients are preload dependent and lack reflex tachycardia, they are very sensitive to vasodilatation and changes in position (Cheng and Day, 2003). Crystalloid and colloids can be used for fluid management. However, the denervated heart will not respond to drugs that act on the autonomic nervous system, such as anticholinergic, anticholinesterase, phenylephrine, or nitroprusside. Additionally, neostigmine can cause severe bradycardia by activation of cholinergic receptors on cardiac ganglionic cells. Alpha- and beta-adrenergic receptors are present in the myocardium; hence endogenous or exogenous catecholamines will increase contractility in response to epinephrine, norepinephrine, isoproterenol, or dobutamine. Conversely, there can be a decrease in contractility in response to beta-blockers (Backman et al., 1997). The effect of beta-blockers, however, may result in severe hypotension, and their use should be avoided.

Left and right ventricular ejection fraction as well as stroke volume are normal in the transplant heart, and will remain so over at least the first 5 years after heart transplantation (Von Scheidt et al., 1991). Normally a higher resting heart rate of 90–100 is present, since the transplanted heart is dependent on preload for inotropy. This is extremely important in the anaesthetic management of these patients, since the normal physiological response to hypovolaemia is absent. On the ECG two P waves may be present: one of the recipient native atrium, which is non-conductive because of the suture lines, and the other from the donor atrium.

These patients frequently present with conduction abnormalities and 5% will require a pacemaker. The management of the pacemaker is similar to that of any other patient, requiring evaluation of proper function and change of pacing mode around the time of the surgical procedure when indicated (Von Scheidt, 1991).

Heart transplant patients will present for endocardial biopsies. Biopsies are usually performed through the right internal jugular vein, thus avoiding catheterization. However, communication with the transplant surgeon regarding the necessity for multiple biopsies during the course of surgery is important (Firestone, 1991).

Anaesthetic considerations in the lung transplant recipient

Lung transplant recipients may require routine bronchoscopic evaluation in the days following transplantation. This is usually done with light sedation (Murthy et al., 2007). In addition, early complications include re-exploration for cardiac tamponade, pleural bleeding, thrombosis, and wound dehiscence. Pulmonary function tests and arterial gas analysis are of special importance in the management of these patients. Patients with lung transplantation require months to achieve total recovery of arterial

oxygenation, but the outcomes have improved markedly in recent years, especially among bilateral lung transplant recipients (Pochettino et al., 2000). These patients will achieve normal arterial oxygenation almost at the time of hospital discharge. In contrast, outcome among single lung transplant recipients is highly dependent on the underlying disease and functionality of the remaining lung. The FEV1 in patients with single lung transplant can increase to 50–60% of the predicted value, but with persistence of a restrictive pattern (Pochettino et al., 2000). Hypercapnia in patients with emphysema and the ventilatory response to fluctuations in $PaCO_2$ is normalized within weeks of lung transplantation.

Careful clinical evaluation of symptoms such as progressive dyspnoea, cough with purulent tracheobronchial secretions, and deterioration of pulmonary function tests indicate bronchiolitis obliterans (BOB), a complication associated with chronic rejection. This condition affects 50–60% of patients who survive 5 years after lung transplantation. It carries a mortality rate of 40% (Feltracco et al., 2011). Any deterioration in oxygen saturation prior to surgery should prompt immediate arterial blood gas evaluation, with postponement of non-emergent surgical procedures.For this reason, arterial line placement is indicated in patients undergoing general endotracheal anaesthesia.

Furthermore, the lung transplant patient may present with tracheal stenosis or a stricture at the site of the tracheal anastomosis. In this case extreme care should be taken during placement of the endotracheal tube when general anaesthesia is warranted (Chacon et al., 1998). During airway manipulation, aseptic technique is recommended. It is important to note that the loss of the cough reflex may predispose these patients to silent aspiration and/or accumulation of secretions (Boscoe, 1995).

In general, the double lung transplanted patient will present with lower overall compliance when compared to normal (Haddow, 1997). In emphysematous patients with single lung transplants, over distention of bullae can produce pneumothorax. In patients with fibrous lung tissue, over inflation of the lung may cause barotrauma (Feltracco et al., 2011). Lung-protective ventilation entails limiting peak inspiratory pressure (PIP) to 30–35 cm/H_2O, plateau pressures to 20–25 cm/H_2O, and tidal volumes <7 mL/kg of predicted ideal body weight, and adjusting respiratory rate to desired $PaCO_2$ (40–45 mmHg).

Cardiopulmonary function will gradually normalize after transplantation, with reduction of pulmonary vascular resistance and pulmonary pressures, increases in cardiac index, and remodelling and improvement of right heart function (Mendelo et al., 2002). During surgery, ideal positioning is lateral decubitus with the transplanted lung in the non-dependent position. The lack of adequate lymphatic drainage of the transplanted lung requires conservative fluid management (Baker et al., 2005).

Postoperative considerations and pain management

Previous organ transplant does not require a mandatory postoperative ICU stay (Mandell et al., 2002). On the contrary, exposure to patients with highly resistant nosocomial infections should be avoided wherever possible. The need for intensive care should be considered on a case-by-case basis, as in any other patient, and will ultimately depend on the patient's medical condition, comorbidities, haemodynamic and oxygenation status, and the complexity of the planned surgical procedure, or mandated by complications encountered during surgery (Haddow and Brock-Utne, 1999).

Extubation is a primary goal in these patients. It decreases the risk of ventilator-associated complications such as barotrauma or ventilator-associated pneumonia. The usual criteria for extubation will apply. However, some authors advocate extubation of lung transplant patients in the lateral decubitus position to prevent aspiration into the graft.

Postoperative analgesia with a multimodal approach to pain management is important to ensure extubation and early ambulation (Siniscalchi et al., 2000). Patient-controlled analgesia should be used where appropriate. However, morphine metabolites may accumulate in patients with impaired renal function. Some transplant patients may have tolerance to opioids due to enzyme induction from previous intravenous drug use or for chronic pain management. This may make perioperative management more complicated. In these patients, multimodal analgesia or the use of ketamine or regional analgesia may be of particular benefit. Epidural or regional analgesia can be used when appropriate, and depends upon institutional preferences as well as postoperative protocols by the acute pain service. Non-steroid anti-inflammatory drugs should be used sparingly, if at all, because of the added risk of nephrotoxicity among patients on immunosuppressive drugs (Harris et al., 1988).

Conclusion

In this chapter we have addressed the perioperative care of the organ transplant patient undergoing non-transplant surgery. We have provided guidelines for each transplanted organ system, the preoperative evaluation and screening necessary to ensure the integrity of the patient with a transplanted organ, as well as the interactions presented by

anaesthesia and immunosuppressive therapies. The population of organ transplant recipients among non-transplant surgical patients is increasing exponentially. One of the important points highlighted in this chapter is the fact that the vast majority of transplant recipients who are scheduled for elective non-transplant surgery are completely functional patients with good quality of life. We have emphasized the importance of a thorough assessment to include a careful review of the health status since transplantation, while taking into account pre-existing comorbidities and the risks associated with the type and scope of the planned surgical procedure. In particular, it is important to assess the type of immunosuppression regimen and their side effects, anaesthetic and drug interactions, as well as graft function.

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