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Anesthetic Considerations in Transplant Recipients for Nontransplant Surgery

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Abstract

As solid organ transplantation increases and patient survival improves, it will become more common for these patients to present for nontransplant surgery. Recipients may present with medical problems unique to the transplant, and important considerations are necessary to keep the transplanted organ functioning. A comprehensive preoperative examination with specific focus on graft functioning is required. The anesthesiologist needs to pay close attention to considerations of immunosuppressive regimens, blood product administration, drug interactions as well as the risk and benefits of invasive monitoring in these immunosuppressed patients. This article reviews the post-transplant physiology and anesthetic considerations for patients after solid organ transplantation.

Keywords: anesthesia methods, intraoperative monitoring, organ transplantation physiology, perioperative care, solid organ transplantation

1. Introduction

The number of solid organ transplants performed worldwide is ever increasing. The improved survival rates are the result of well-established surgical techniques and effective immunosuppressive therapy. All this has led to an increase in number of patients who present for either elective or emergency non-transplant surgery [1, 2]. Laparotomy for small bowel obstruction, hip arthroplasty given the increased risk of fracture and avascular necrosis as a result of chronic steroid use causing bone demineralization and osteoporosis, lymph node excision and biopsy because of increased risk of lymphoproliferative disease, native nephrectomy in kidney transplant recipients, bronchoscopy in lung recipients, biliary tract interventions in liver recipients, and abscess drainage because of increased risk of infection are just a few of

the increased surgical needs in this population. These patients cannot always return to the transplant facility for surgery, so it is incumbent on all anesthesiologists to review perioperative issues associated with transplantation.

Perioperative anesthetic management in majority of recipients is similar to the standard practice for any patient. However, we must bear in mind some essential considerations: problems of allograft denervation, the adverse effects of immunosuppression and its interaction with anesthetic drugs, the risk of infection, and the potential for organ rejection. When transplant recipients require nontransplant surgery, immune competence can be altered from the stress of surgery, acute illness, or disruption of the regimen by inexperienced providers [3].

Preoperative assessment of any transplant recipient undergoing non-cardiac surgery should focus on graft function and rejection, risks of infection, and function of other organs, particularly those that may be compromised due to either immunosuppressive therapy or dysfunction of the transplanted organ itself and drug interactions. There is no ideal anesthetic for use in organ transplant recipients. However, certain principles can be applied to all transplant patients who undergo anesthesia and surgery [4].

In this chapter, we will give an overview of immunosuppressive therapy and its interaction with anesthetic drugs as well as considerations regarding specific transplanted organs (heart, lungs, liver, kidney, pancreas, and intestine).

2. Immunosuppression

2.1. Immunosuppression protocol

Transplant patients are always under various regimens of immunosuppressive therapy (Table 1). Immunosuppression trends for solid organ transplantation have undergone a perceptible shift over the past decade. There are broad therapeutic patterns and numerous immunosuppressive protocols depending on transplanted organ, as well as the regional differences (country, hospital). However, some strategies are similar. We distinguish induction immunosuppressive therapy and maintenance of immunosuppressive therapy. Induction of immunosuppression begins immediately before the organ implantation. Antibodies are prescribed for the majority of kidney, pancreas, and intestine recipients and for just under half of thoracic organ recipients. It is extremely uncommon in liver transplantation [5]. Maintenance of immunosuppression involves one of the drugs from each group: calcineurin inhibitors (CNI), antimetabolites, and steroids.

The immunosuppressant strategy has been changing over the years. CNIs are still being used for the maintenance of immunosuppressive therapy, though shifting from cyclosporine to tacrolimus is being observed [6]. Modifications are also made among antimetabolites, from azathioprine to mycophenolate mofetil, and it is more common to decrease corticosteroid use or even implement steroid-free protocol in suitable transplant recipients [7, 8].

Most of the commonly used immunosuppressants have a narrow therapeutic index and display significant variability in blood concentrations between individuals. In transplant recipients,

| General names | Generic names | Brand names |
|--|---|--|
| Corticosteroids | Prednisone Methylprednisolone | |
| Calcineurin inhibitors | Tacrolimus (or FK-506) Cyclosporine (or cyclosporine A) | Prograf Sandimmune, Neoral, Gengraf, Eon, SangCya, generic cyclosporine |
| Antimetabolites | Azathioprine Cyclophosphamide Mycophenolate mofetil Mycophenolate sodium | Imuran Cytoxan, Neosar CellCept Myfortic |
| Polyclonal antibodies | Antithymocyte globulin (rabbit) Antithymocyte globulin (equine) NRATG, NRATS, ALG | Thymoglobulin ATGAM |
| Anti-CD3 monoclonal antibodies | Muromonab-CD3 | Orthoclone OKT3 |
| Anti-CD52 monoclonal antibodies | Alemtuzumab | Campath |
| Anti-IL-2 receptor monoclonal antibodies | Basiliximab Daclizumab | Simulect Zenapax |
| TOR inhibitors (or rapamycin) | Sirolimus | Rapamune |

Table 1. Most commonly used immunosuppressive drugs.

both supratherapeutic and subtherapeutic drug concentrations can have devastating results. Subtherapeutic levels increase the risk of transplant rejection, and supratherapeutic levels (overimmunosuppression) can lead to infection and/or drug-specific side effects. Importantly, the incidence of acute rejection has declined over the past decade. Treatments for acute rejection continue to include high-dose corticosteroid and antibody therapies [9].

2.2. Side effects and drug interactions

Chronic immunosuppressive therapy has its adverse effects such as lowered seizure threshold, diabetes, hypertension, hyperlipoproteinemia, decreased glomerular filtration, hyperkalemia, hypomagnesemia, increased risk of infection and tumors, pancytopenia, osteoporosis, and poor wound healing. This may have some impact on perioperative management and choice of anesthetic agents (**Table 2**) [10].

The blood level of both cyclosporine and tacrolimus must be kept within the indicated therapeutic range to get the desired effect. The perioperative fluctuation of the plasma level of these two drugs should be strictly monitored. There is a significant reduction of drug blood level by dilution with volume infusion or cardiopulmonary bypass in cardiac surgery [11]. Both these drugs are metabolized by cytochrome P-450 system of liver, and therefore many of the drugs administered perioperatively can affect their plasma levels [12, 13]. A better understanding of

| CyA | Tac | Aza | Ster | MMF | ATG | OKT3 | |
|---------------------|-----|-----|------|-----|-----|------|---|
| Anemia | - | - | + | - | + | - | - |
| Leucopenia | - | - | ++ | - | + | + | + |
| Thrombocytopenia | - | - | - | - | + | - | - |
| Hypertension | ++ | + | - | + | - | - | - |
| Diabetes | + | ++ | - | ++ | - | - | - |
| Neurotoxicity | + | + | - | + | - | - | - |
| Renal insufficiency | + | ++ | - | - | - | - | - |
| Anaphylaxis | - | - | - | - | - | + | + |
| Fever | - | - | - | - | - | + | + |

ATG = anti-thymocyte globulin; Aza = azathioprine; CyA = cyclosporine A; MMF = mycophenolate mofetil; OKT3 = monoclonal antibodies directed against CD-3 antigen on the surface of human T-lymphocytes; Ster = steroids; and Tac = tacrolimus.

Table 2. Side effects of immunosuppressive that have direct impact on anesthetic and perioperative management [1].

pharmacokinetics over the years, allows now days a reduction of immunosuppressant dose in elderly patients while maintaining the therapeutic level [14].

In the hospital settings, almost 3–5% of adverse drug reactions are due to drug-drug interactions. It is estimated that the percentage is even higher in solid organ transplant recipients dependent on immunosuppressive therapy. Reactions can be among two immunosuppressants or between the immunosuppressant and other drugs [15]. Due to the fact that the administration of cyclosporine (CyA) and tacrolimus (Tac) is ever increasing, we give an overview of their interaction with other drugs (**Table 3**).

During anesthesia, we provide a range of drugs from different groups, which increase the possibility of drug interaction and thus potentially endanger the patient in the perioperative period. One should keep in mind that many pharmacokinetic and pharmacodynamic interactions can occur among the drugs that patients take after transplantation, due to cytochrome P450 enzyme system induction or inhibition by another drug. There are few data concerning interaction between immunosuppressive drugs and anesthetic agents. Most of the evidence is based on clinical practice and occasional case reports or case studies. Large randomized controlled trials involving either general or regional anesthesia are still lacking. **Table 4** describes the effect of various anesthetic agents on immunosuppressant and vice versa.

Data on the effects of general anesthesia on cyclosporine or tacrolimus pharmacokinetics in humans are limited. Most of the inhalational anesthetic agents are well tolerated unless there is a significant heart failure. However, caution is advised in concurrent administration of oral cyclosporine and isoflurane anesthesia. Subtherapeutic blood levels have been reported in patients who received peroral drug form less than 4 hours preoperatively. It is probably due to a reduction in gastric emptying and absorption from the proximal small bowel, which can occur during isoflurane anesthesia [16]. Steady-state blood levels of cyclosporine and cyclosporine clearance are not altered by isoflurane/nitrous oxide anesthesia in animal model [17].

| Drug class | Drug | Effect on blood level Adverse effect |
|--|--|--|
| Benzodiazepines | Diazepam, midazolam, alprazolam, flurazepam, clonazepam | ↑ Benzodiazepines |
| Antibiotics | Erythromycin, metronidazole, norfloxacin, levofloxacin | ↑ CyA and Tac level |
| Antimicrobial | Rifampicin | ↓ CyA and Tac level |
| Antimalarial | Chloroquine, mefloquine | ↑ CyA and Tac level |
| Antifungal | Ketoconazole, fluconazole, itraconazole, voriconazole, amphotericin B | ↑ CyA and Tac level Renal dysfunction |
| Anti-retroviral | Ritonavir, atazanavir, darunavir, cobicistat, delaviridine | ↑ CyA and Tac level |
| Cardiovascular drugs (antiarrhythmics and calcium channel blocker) | Amiodarone, lidocaine, quinidine, verapamil, diltiazem, amlodipine, felodipine | ↑ CyA and Tac level QT prolongation by amiodarone and quinidine |
| Statins | Simvastatin, atorvastatin, lovastatin, pravastatin | ↑ Statin concentration |
| Anticoagulants | Apixaban, dabigatran, rivaroxaban | ↑ Anticoagulant concentration |
| Oral hypoglycemics | Sulfonylurea, biguanides | ↑ CyA level |
| Gastrointestinal | Metoclopramide, omeprazole, lansoprazole, octreotide, cimetidine, ranitidine | ↑ CyA and Tac level Renal dysfunction QT prolongation by octreotide with Tac |
| Analgesics | Nonsteroidal anti-inflammatory drugs | ↑ CyA and Tac level Renal dysfunction |
| Antipsychotics | Haloperidol, desipramine, fluoxetine, trazodone, pimozide | ↑ CyA and Tac level ↑ Pimozide level |
| Hormones | Estrogen and testosterone preparation | ↑ CyA and Tac level |
| Others | Bosentan, carbamazepine | ↓ CyA and Tac level |

CyA = cyclosporine A; Tac = tacrolimus.

Table 3. Drugs that interact with cyclosporine A and tacrolimus.

Cyclosporine and tacrolimus increase blood level of benzodiazepines. Transplanted patients need dose modification [12, 13]. Propofol infusion does not modify the cyclosporine concentration. It is considered to be a suitable agent for intravenous anesthesia in cyclosporine-treated patients, provided a close postoperative monitoring of cyclosporine blood concentrations is maintained [18]. Cyclosporine tends to increase the analgesic effect produced by fentanyl, but the mechanism is unclear [19].

Most of relaxants can be used safely. Cyclosporine enhances the effects of muscle relaxants. Prolonged neuromuscular block in patients receiving cyclosporine after vecuronium and pancuronium administration has been described [20, 21]. Atracurium and cisatracurium

| Anesthetic agent | Effect with immunosuppressive drugs |
|-------------------|--|
| Isoflurane | ↓ Clearance of oral CyA |
| Thiopental | Nil |
| Benzodiazepines | ↑ Blood level of benzodiazepines |
| Propofol | Nil |
| Etomidate | Nil |
| Opioids | CyA ↑ analgesic effect produced by fentanyl |
| Muscle relaxants | Prolonged neuromuscular blockade |
| Neostigmine | Caution in heart transplant patients |
| Local anesthetics | Bupivacaine and ropivacaine can be safely used |

Table 4. Effect of specific anesthetic agent on immunosuppressive drugs.

are preferred agents because their elimination is not affected by renal or hepatic function. Therefore, patients receiving cyclosporine as immunosuppressive therapy may require a smaller dose of nondepolarizing muscle relaxant and the recovery time may be prolonged [22]. Neostigmine can lead to bradycardia and cardiac arrest in patients with heart transplantation despite the concurrent use of an antimuscarinic agent [23]. Bupivacaine and ropivacaine can be safely used through regional routes without any side effects [24, 25].

3. Anesthesia and preoperative care

3.1. Preoperative assessment of transplant recipients

Many transplant recipients live relatively normal and productive lives, but often have limited physical reserves. A successful transplant abolishes the symptoms and replaces function of the failed organ, but often there are persistent abnormalities from the underlying or pre-existing illness that may have caused the organ failure or chronic physiologic abnormalities resulting from the organ failure itself. The preoperative evaluation of transplant recipients undergoing non-transplant surgery should include graft function, signs of rejection, presence of infection, and function of other organs.

Allograft rejection may occur at any time during the post-transplant period, especially when discontinuing the use of immunosuppressants. Chronic rejection is the most significant medical obstacle to long-term morbidity-free allograft survival. The incidence is thought to progressively increase with time after transplantation, but after a period of 5 years, it affects about 10% of liver to around 60% of lung allograft recipients [26]. Chronic organ rejection results in a progressive deterioration of organ function (assessed through laboratory tests) and is the main cause of late mortality in the transplant recipients. Mortality rate is high if rejection remains untreated before surgery [27]. Therefore, the presence of any degree of rejection should be ruled out and urgently managed preoperatively with increased immunosuppression.

Immunosuppressed patients are at risk of infections that may be bacterial, viral, fungal, or protozoan. Infection is a significant cause of morbidity and mortality after transplantation [28]. Its presence should also always be preoperatively ruled out (by obtaining laboratory, radiologic, and microbiology tests). It is imperative to emphasize that the immunosuppressed patient may not present the typical signs and symptoms of infection (i.e. fever, leukocytosis). Microbiology advice should be strongly sought for prevention as well as strict control of infection. Any infection should be treated preoperatively [29].

Although transplant patients are considered as risk hosts for infection because of their immune status, there is no evidence to suggest different bacteriology of surgical site infections than for the general population. Antimicrobial coverage need not be expanded to include atypical or opportunistic organisms as long as active infection with such an organism is not present or suspected [30]. Prophylaxis with broad spectrum antibiotic should be administered 1 hour before surgical incision (depending on hospital protocol) (Table 5).

Transplanted patients may also suffer from diabetes, hypertension, epilepsy, renal dysfunction, bone marrow suppression, lymphoproliferative disorders, and adrenal insufficiency as the side effects of chronic immunosuppressive therapy [31]. Hepatobiliary and pancreatic diseases are relatively common after transplantation, as well as the upper gastrointestinal bleeding secondary to peptic ulcer disease. Surgical stress, corticosteroids, and mycophenolate may contribute to gastrointestinal ulcers [32]. So, it is absolutely necessary to provide stress ulcer prophylaxis for transplanted patients.

The transplant patient population is considered as high-risk group for developing venous thromboembolism (VTE) given the fact that most of these patients have multiple identifiable risk factors [33]. However, the exact risk of developing VTEs in these patients is not clearly defined in the literature, nor there are clear guidelines regarding the appropriate use of thromboprophylaxis in transplant recipients [34]. In our opinion, VTE prophylaxis should be tailored to the patient's specific needs in accordance with current guidelines [35].

| Operation | Recommended antibiotic prophylaxis |
|-----------------------------------|---|
| Cardiothoracic surgery | Cefazolin, cefuroxime, or cefamandole. If patient has a β -lactam allergy: vancomycin or clindamycin |
| Vascular surgery | Cefazolin or cefuroxime. If patient has a β -lactam allergy: vancomycin with or without gentamycin, or clindamycin |
| Colon surgery | Oral: neomycin plus erythromycin base, or neomycin plus metronidazole. Parenteral: cefoxitin or cefotetan, or cefazolin plus metronidazole |
| Hip or knee arthroplasty | Cefazolin or cefuroxime. If the patient has a β -lactam allergy: vancomycin or clindamycin |
| Vaginal or abdominal hysterectomy | Cefazolin, cefotetan, cefoxitin or cefuroxime |

Table 5. Antimicrobial prophylaxis for selected surgical procedures [30].

3.2. Preoperative assessment and premedication

The transplant team as well as the attending anesthesiologist and surgeon should have a good coordination during perioperative period, especially if a major surgical procedure is planned. A comprehensive preoperative evaluation by the anesthesiologist should include: evaluation of the graft function, presence of infection, function of other organ systems, the presence of concomitant diseases as well as the preoperative performance or functional status. Adherence to the fundamental principles of preoperative evaluation along with a high level of vigilance is required. Information and medical history should be gathered from the medical records, interview with the patient and/or next of kin or guardian. If medical information is unavailable, attempts should be made to contact the transplant center for pertinent history. Other useful information from the transplant center includes their most recent evaluations and recent data on graft function and general health of the patient. Close communication with the transplant team may be the single most important step in preparing the patient for surgery and developing a perioperative anesthetic plan.

A thorough review of systems along with a physical examination is essential in this population. Findings such as recent weight gain, edema, dyspnea, sweats, malaise, fever, rashes, abdominal pain, abnormal breath sounds on auscultation, and changes in stool or urine output are some of the potential signs and symptoms of infection or rejection.

The following investigations should be available preoperatively.

1. Laboratory parameters:
 - a. Complete blood count (to rule out bone marrow suppression)
 - b. Electrolytes
 - c. Renal function tests
 - d. Liver function tests
 - e. Coagulation tests
 - f. Biomarkers (i.e. brain natriuretic peptide)
2. Chest radiograph
3. Electrocardiogram
4. Echocardiography
5. Miscellaneous: depending on the type of surgery and transplanted organ (i.e. coronary angiography, stress test, spirometry, biopsy)

Each preoperative evaluation and testing should be considered individually based on the target organ system(s) to be evaluated, the patient's medical history, and the inherent risks of the upcoming surgical procedure.

Cardiovascular disease is a major cause of mortality and morbidity among organ transplant recipients, especially in those with chronic kidney disease or previous heart transplant, making

the risk of a perioperative cardiovascular event a legitimate concern. Many transplant recipients have undergone complete cardiac testing and in some cases, interventions, before their transplant surgery. Records of the testing and interventions can be easily obtained from the transplant center to be used for comparison and consideration before the upcoming surgery. We must also bear in mind that many of these patients may have asymptomatic coronary disease as a result of diabetes or the transplant itself [36].

If unexpected abnormal findings are identified on physical examination or laboratory testing, symptomatic changes outside the patient's baseline are documented, or suspicion for rejection or infection exists during the preoperative evaluation, it should be considered to postpone any surgery that is non-urgent or elective. The patient should also be expeditiously referred back to the transplant center, cardiologist, or other consulting physician as indicated.

Standard premedication may be used, as in non-transplant patients. However, dose adjustment for some drugs is needed (**Table 3**). Antibiotic, stress ulcer and VTE prophylaxis administration is recommended (as mentioned above). Supplemental steroids are not necessary for stress coverage except in post-transplant recipients in whom steroids are recently withdrawn [37].

Post-transplantation diabetes mellitus is a common metabolic consequence of the agents of immunosuppressive therapy agents [38]. It is imperative to institute a glycemic control plan before the surgery with closely managing intraoperative and postoperative glucose control.

The dose of immunosuppressive drugs should not be altered and should be continued postoperatively to reduce the risk of rejection. Daily monitoring of the steady-state blood level is recommended. Oral cyclosporine should be administered 4–6 h before surgery to maintain therapeutic blood levels. The alteration of dose of other immunosuppressive drugs dose is not required unless the route of administration needs to be changed from oral to intravenous [39].

3.3. General anesthetic considerations

There is no ideal anesthetic plan that can be used for all transplant recipients undergoing non-transplant surgery. A variety of anesthetic techniques have been successfully used in patients with a transplant history including general (inhalational, balanced, and total intravenous), neuraxial, and regional anesthesia.

3.3.1. Monitoring

Generally, invasive monitoring is not mandatory and anesthesia should be performed using standard European Society of Anesthesiology's monitoring guidelines [40]. The decision to use invasive hemodynamic monitors, placement of central venous access, pulmonary artery catheters, or other procedures such as transesophageal echocardiography should be made on a case-by-case basis. It should be guided by consideration of the patient's comorbidities, hemodynamic stability, the expertise of the anesthesiologist in placing the invasive devices, and by the type of surgery and anesthesia planned. Aseptic technique is of utmost importance to minimize exposure to infectious organisms and bacteremia when attempting any invasive procedures in this population [41].

3.3.2. Airway management

Airway management of transplant patients may pose a concern for several reasons. Many patients may have pre-existing diabetes mellitus before transplant or acquire diabetes after transplant. Diabetic patients can develop limitations in joint mobility caused by glycosylation of the connective tissue within their joints [38]. This population is also at increased risk for lymphoproliferative disorders secondary to immunosuppressant drugs, and lymphoproliferative growth may compromise any part of the airway or mediastinum and cause life-threatening airway obstruction during sedation and anesthesia [41]. Gingival hyperplasia is present at times in patients taking cyclosporine and it may lead to bleeding during airway manipulation. Aspiration risk may be increased in transplanted patients as a result of delayed gastric emptying and gastropathy [32]. These potential problems should all be taken into consideration when constructing the anesthetic plan for airway management.

Oral endotracheal intubation is preferred over nasal intubation because of the potential of infection caused by nasal flora [42]. The use of a laryngeal mask is acceptable (within its indications) [43]. Keep in mind that laryngoscopy and tracheal intubation may not produce a sympathetic response secondary to the loss of cardiac baroreceptor reflexes in heart transplanted patients [44]. Avoid hyperventilation in patients taking cyclosporine and tacrolimus because of a decrease in seizure threshold with these two drugs. Early postoperative extubation is preferred if possible to prevent the development of nosocomial or ventilator-associated pneumonia [45].

3.3.3. General anesthesia

All inhalational and intravenous anesthetics have been used with success in transplant recipients. The choice of anesthetics and adjunctive drugs should be determined by the type of surgery and condition of the patient. As a general guideline, if hepatic and renal functions are normal, all standard anesthetic medications and adjuncts may be used. Some special considerations for each type of organ transplant are discussed in the section on organ-specific considerations.

3.3.3.1. Intravenous anesthetics

The selection and administration of intravenous anesthetics should be guided by the patient's hemodynamic status, the drug's cardiovascular effects, and pharmacokinetic properties. Premedication with benzodiazepines is acceptable. Caution should be used in patients with hepatic or renal insufficiency as effects may be prolonged. Also, the dose of barbiturates should be adjusted in patients with hepatic insufficiency to avoid prolonged effects.

Propofol is extensively metabolized by the liver to inactive glucuronic acid metabolites that are excreted by the kidneys. Nevertheless, there seems to be no need for dose adjustments in patients with hepatic or renal failure indicating an extrahepatic route of elimination as well [46]. Caution should be used in patients with cardiovascular compromise as propofol can worsen cardiac contractility, compromise cardiac preload, cause bradycardia, and lower systemic vascular resistance culminating in diminished cardiac output and mean arterial pressure.

Etomidate does not have the cardiac depressant effect of barbiturates and propofol. Etomidate is metabolized rapidly by hydrolysis within the liver and by plasma esterases and also does not require dosage adjustment in renal or hepatic disease. One unique characteristic of etomidate is its ability to inhibit enzyme necessary for the synthesis of cortisol [47]. This may have clinical significance in patients who already have adrenal suppression as a result of exogenous corticosteroid use.

Ketamine is metabolized via the hepatic cytochrome P-450 system. Therefore, the clinical effects of ketamine are prolonged in the presence of hepatic insufficiency. The usual cardiac stimulating effects caused by central stimulation of the sympathetic system are not present in the denervated heart, but ketamine can still increase systemic vascular tone. Ketamine has neuroexcitatory effects and is known to cause myoclonic activity. It would be wisely to proceed with caution if the ketamine is administered in patients who simultaneously take cyclosporin due to its potential for neurotoxicity.

3.3.3.2. Inhalational anesthetics

All inhaled anesthetics have been used in transplanted patients with success. Although halothane is nowadays rarely used, nevertheless it is necessary to mention its potential for hepatotoxicity and direct cardiac depressant effects. Most commonly used volatile anesthetics are isoflurane, sevoflurane, and desflurane. There does not seem to be a significant clinical advantage or disadvantage of one over the others. The choice of inhaled anesthetic can be dictated by the anesthesiologist's preference, experiences, and comfort with the anesthetic [48]. It is probably prudent to avoid prolonged use of N₂O because of the potential risk of bone marrow suppression and the potential for altered immunologic response [49].

3.3.3.3. Opioids

Fentanyl is suitable and safe for short-term use during surgery. However, if used for long duration, the pharmacodynamic effects should be monitored due to accumulation effect. Reduced renal and liver function does not significantly alter the clearance and half-life of sufentanil. Tissue and blood esterases mainly metabolize remifentanyl and its metabolite, excreted via kidneys, has low potency [50].

Among opioids used for postoperative pain treatment (morphine, codeine, oxycodone, and tramadol) have to be used with caution. Some of their active metabolites accumulate in renal failure and can mediate CNS and respiratory depression. Transdermal buprenorphine and methadone appear to be safe to use even in patients with renal dysfunction [51].

3.3.3.4. Neuromuscular blockade

The decision to use neuromuscular blockade should be based on the type of surgery and actual need for muscle relaxation during the procedure or the need to optimize intubating conditions. The choice of specific neuromuscular blocking agent should be dictated by length of surgery, underlying medical illnesses (i.e. myasthenia or other neuromuscular disorders), history of malignant hyperthermia, and the functional state of the patient's kidney and liver.

In the group of non-depolarizing drugs, it is preferable to use short-acting relaxants (mivacurium) or intermediate-acting agents independent of kidney and liver function (cisatracurium, atracurium). Vecuronium, rocuronium, and pancuronium can have prolonged effects in the face of hepatic or renal insufficiency. They require dose adjustments, close neuromuscular monitoring, and evidence of full reversal before extubation [52]. Some immunosuppressive drugs (i.e. azathioprine and cyclosporine) can prolong the action of the neuromuscular blocking agents [22].

Succinylcholine, the only depolarizing agent available, can be used in organ transplant recipients in the need for rapid sequence intubation and rapid airway control. It should be avoided only if there are other clinical reasons, such as hyperkalemia, muscular dystrophy, or history of malignant hyperthermia [53].

3.3.3.5. *Anticholinesterase drugs*

Most of the cholinesterase inhibitor drugs are eliminated through the kidneys (neostigmine, edrophonium, and pyridostigmine). Caution is advised in renal failure. Several reports described that neostigmine may produce a dose-dependent life-threatening bradycardia in heart transplant recipients, whereas another publication described the safe use of neostigmine [54]. Reversal of neuromuscular block with sugammadex is another possibility, but limited data exist in literature [55].

3.3.4. *Regional and neuraxial anesthesia*

The decision to perform a regional or neuraxial anesthetic technique in a previously transplanted patient must be made on an individual basis. We must carefully consider potential benefit and risks of these techniques as well as the anesthetic alternatives when constructing the anesthetic plan in this population. There may be several advantages to choosing a neuraxial or regional technique in this population. Superior analgesia over systemic opioids, especially in patients who may have narcotics tolerance as a result of long-term opioid use, reduced pulmonary complications, and decreased incidence of graft occlusion are just a few of the benefits of regional and neuraxial anesthesia [56]. Clinically relevant doses of bupivacaine and ropivacaine, which are commonly used local anesthetics for neuraxial anesthesia, do not seem to result in toxic levels or increased risk of toxic effects in renal and liver transplant recipients. However, it is important to be prepared for the risk of hypotension because of pre-existing autonomic neuropathy and cardiac denervation in this population. Cautious correction of hypovolemia before epidural or spinal anesthesia may help to attenuate the hypotension. Concurrent hemodynamic monitoring is imperative during the procedure. Direct and indirect-acting adrenergic agonists should be readily available along with emergency airway supplies.

The consideration of spinal or epidural anesthesia is appropriate in this population as long as there is no increased risk for bleeding complications. It is necessary to perform a total blood count to exclude bone marrow suppression, especially thrombocytopenia, and coagulation tests (PT, INR, APTT, and fibrinogen). Peripheral nerve blocks became popular anesthetic option due to hemodynamic stability and better postoperative analgesia. Some studies show no difference in duration of peripheral nerve blocks in patients after transplantation compared to the general surgical population [57, 58]. Nevertheless, large prospective randomized trials are still lacking.

Although the risk of infectious complications is very low, it is important to be highly vigilant when monitoring these patients after a neuraxial anesthesia as the attenuated inflammatory response may diminish the typical signs and symptoms of infection [59]. Again, aseptic technique and a mask should be considered essential when performing these procedures.

3.3.5. Postoperative care management

Regardless of the procedure performed, successful outcomes also depend on optimal postoperative care. Depending on the type of surgery, patients' comorbidities, and preoperative condition, patient is after surgery transferred either to intensive care unit (ICU) or post-anesthesia care unit (PACU). Adequate monitoring is tailored accordingly [60]. We reduce the delirium incidence by minimizing sedation, speed up extubation, and facilitate early ambulation and physical rehabilitation. Appropriate analgesia is essential component of postoperative surgical care. Opioids are the mainstay of analgesia in the early postoperative phase after major surgery. Parenteral paracetamol is an effective analgesic agent and may spare narcotics. There is no evidence of an increased risk of hepatotoxicity [61]. Once extubated, patient-controlled analgesia (PCA) devices are effective and well received by patients and nurses. Non-steroidal anti-inflammatory drugs should be avoided because of the risk of adverse interactions (e.g., gastrointestinal hemorrhage, nephrotoxicity, hepatic dysfunction). They augment nephrotoxicity of cyclosporine, as both drugs affect the renal microcirculation [62, 63].

Immunosuppressive therapy should be continued during the perioperative period and daily monitoring of steady-state cyclosporine or tacrolimus blood levels is recommended [64]. The dose of other immunosuppressive drugs should not be altered perioperatively unless the route of administration needs to be changed from oral to intravenous. In addition to the routine care as those for non-transplant recipients, increased attention should be paid to the preload status, renal function, and prevention of infection.

4. Specific anesthetic considerations

4.1. Heart transplant recipients

Transplanted heart is completely denervated, meaning it lacks neural regulating mechanisms [65]. Even though, it has the ability to adjust with compensatory mechanisms to the increased demands in stress returning the recipients to an active life. Transplanted heart has no sensory sympathetic and parasympathetic innervation. Therefore, it has a higher resting heart rate of 90–110 bpm secondary to the loss of vagal tone. The resting ECG is commonly altered showing two P waves: one is from the recipients' own SA node and the other is the donors' SA node. Patients are at higher risk of developing atrial flutter or atrial fibrillation. The transplanted heart is "preload dependent." Cardiac output becomes dependent on venous return. Therefore, it is important to maintain a sufficient systolic pressure and prevent hypovolemia [66].

Although the cardiac index of the transplanted heart is lower than that of normally innervated control hearts, it remains in the normal range. The catecholamine response is different from

that of normal heart because intact sympathetic nerves are required for the normal uptake and metabolism of catecholamines. The receptor density, however, remains unchanged, and the transplanted heart can respond to direct-acting drugs (adrenaline and noradrenaline) [67]. Isoprenaline and dobutamine have similar effects in both transplanted and normal heart. Because atropine has no effect on a transplanted heart, isoprenaline and adrenaline should be readily available to manage bradycardia and hypotensive emergencies. In recent years, milrinone and levosimendan, inotropic vasodilators, have been included in the pharmacological arsenal. These drugs increase myocardial contractility without myocardial oxygen consumption (unlike catecholamines). In addition, they lead to arterial and venous vasodilatation and afterload decrease [68, 69]. **Table 6** summarizes the hemodynamic response of some commonly used drugs for resuscitation.

Heart transplant recipients may present with ongoing rejection with myocardial dysfunction, accelerated coronary atherosclerosis, or severe dysrhythmias, all of which must be diagnosed before surgery. Chronic allograft rejection usually presents as accelerated coronary artery disease. Therefore, heart transplant recipients may have significant myocardial ischemia without any clinical symptoms of pain and silent myocardial infarction on the ECG. Severe rejection can lead to significant systolic and diastolic dysfunction [70, 71].

General anesthesia is usually preferred, as there is a possibility of impaired response to hypotension after spinal or epidural anesthesia. A goal of anesthesia in this setting is the avoidance of significant vasodilation and acute decrease of the preload. Invasive hemodynamic monitoring is extremely useful during surgery that involves large volume shifts, due to the fact that these patients are preload-dependent and may be prone to myocardial dysfunction and/or

| Drugs | SA node rate | AV conduction | SVR | BP | CO | Remark |
|---------------|--------------|---------------|-----|----|----|--|
| Atropine | 0 | 0 | 0 | 0 | 0 | Cannot be used in bradycardia |
| Dopamine | ↑ | ↑ | 0 | E | ↑ | |
| Dobutamine | ↑ | ↑ | 0 | ↑ | ↑ | Effect on HR is more than normal heart |
| Adrenaline | ↑ | ↑ | 0 | ↑ | ↑ | |
| Noradrenaline | ↑ | ↑ | 0 | ↑ | E | |
| Isoprenaline | ↑ | ↑ | 0 | ↓ | ↑ | |
| Phenylephrine | 0 | 0 | 0 | ↑ | E | |
| Digoxin | 0 | ↓ | | | | |
| Milrinone | 0 | 0 | ↓ | ↑ | ↑ | |
| Levosimendan | 0 | 0 | ↓ | ↑ | ↑ | |

SA – sinoatrial; V – atrioventricular; SVR – systemic vascular resistance; BP – blood pressure; CO – cardiac output; HR – heart rate; 0 – no effect; and E – equivocal.

Table 6. Response of denervated heart to various cardiovascular drugs.

ischemia. Instead of invasive monitoring, intraoperative transesophageal echocardiography may be considered [72, 73]. All preoperative drug therapy should be continued during the perioperative period. If a pacemaker is in place, its proper function should be confirmed.

4.2. Lung transplant recipients

Denervation of the lungs after transplantation is associated with a lack of cough reflex below the tracheal anastomosis level and are unable to clear secretions unless they are awake. Therefore, they are prone to retention of secretions and silent aspiration [74]. These conditions may lead potential hazardous conditions especially in general anesthesia, such as bronchoconstriction and the increased risk of chest infection. In light of potential complications, it is preferable to perform a regional anesthesia whenever possible and if there is no contraindication [75].

Before elective surgery patients should undergo chest radiograph and spirometry to exclude chronic rejection and infection [76]. If allograft rejection or infection is suspected, elective surgery should be postponed and appropriate investigations should be performed.

Altered lymphatic drainage in the transplanted lung may cause interstitial fluid accumulation. It has been recommended that these patients be treated with diuretics and limited crystalloid infusion [77, 78]. Invasive hemodynamic monitoring is often required in heart-lung transplant recipients since there is a narrow line between the pulmonary edema occurrence and maintaining cardiac output with fluid load [79].

4.3. Kidney transplant recipients

Kidney transplant recipient have high incidence of cardiovascular diseases, especially elderly patients with diabetes and after years of dialysis procedures. Spectrum of disease can range from hypertension to severe coronary disease. It is wisely to approach them with caution. Cardiovascular complications are the leading cause of death in renal transplant recipients, accounting for 32% of all deaths [80].

After successful transplantation, renal function is restored, with no need for renal replacement therapy. Still, beware of prolonged drug action and excretion in kidney transplant recipients, due to the fact that their glomerular filtration rate and effective plasma flow can be significantly lower than in healthy subjects [81].

You should suspect at chronic graft rejection when azotemia, proteinuria, and hypertension are seen [82, 83]. One of the important parameters to consider in the prevention of graft failure is the maintenance of appropriate renal perfusion pressure. Perioperative fluid management must ensure restoration and maintenance of intravascular volume, in order to obtain good graft function. Diuretics should not be given without careful evaluation of the patient's volume status.

In anesthetic management, it is prudent to choose drugs that do not rely on the kidney for excretion. Nephrotoxic drugs should be avoided [84]. Cardiovascular instability can be present after a recipient has been recently hemodialysed due to hypovolemia and hypokalemia, causing arrhythmias and increased susceptibility to muscle relaxants [85].

4.4. Liver transplant recipients

Liver synthetic tests should normalize over time pointing out a good liver graft function. There is also gradual decrease of all liver enzyme levels, as graft function becomes normal. Recovery of drug metabolism capacity occurs immediately after reperfusion of the liver graft. Liver transplantation itself results in reversal of the hyperdynamic state that characterizes patients with end-stage liver disease and cardiac performance improves in the months after transplantation. Hypoxemia caused by ventilation/perfusion mismatch is reversed over the course of the first postoperative months. Patients with pre-existing true shunts may require more time to achieve reversal of hypoxemia, or hypoxemia may not resolve at all [86]. Hepatorenal syndrome gradually diminishes, renal function improves over time, and creatinine level may become normal. However, kidneys are still in danger of injury due to immunosuppression side effects [87].

The most severe complication of liver transplantation is hepatic artery thrombosis. It has often been associated with massive transfusion of blood products leading to hemoconcentration. Therefore, liver transplant recipients should have minimal blood viscosity (hematocrit approximately 28%) during the perioperative period [88].

No individual general anesthetic agents are contraindicated when hepatic and renal function is normal. If an epidural or spinal anesthesia is planned, clotting studies and platelet counts should be normal. Neither regional nor general anesthetic techniques were associated with deterioration of liver function assuming proper anesthetic and intensive care management [3, 25].

4.5. Pancreas transplant recipients

Pancreas transplantation provides the most effective method of glycemic and metabolic control. It can be done as a single organ transplant or simultaneously with kidney (predominantly in type 1 diabetes) (SPKT). SPKT is a treatment of choice for uremic diabetic patients when a living-related kidney donor is unavailable. After successful transplantation, pancreas transplant recipients do not require insulin to compensate for the stress response to surgery [89].

However, due to long-lasting diabetes effect, these patients are in high risk of developing cardiovascular diseases. It is prudent to manage these patients with the assumption that they have coronary artery disease [90]. Pancreas recipients still have persistent complications of diabetes such as gastropathy and neuropathy. Aspiration risk may be increased as a result of delayed gastric emptying. This population is also at increased risk for lymphoproliferative disorders secondary to immunosuppressant drugs and lymphoproliferative growth may compromise any part of the airway or mediastinum and cause life-threatening airway obstruction during sedation and anesthesia [91].

Amylase levels in serum and urine should be closely monitored. They can be our only window in the graft rejection recognition [92]. Glucose levels should also be monitored perioperatively. In normal functioning grafts, the suppression of endogenous insulin secretion during hypoglycemia is sufficient to enable a normal glucagon response from the transplanted pancreas, even in surgical stress [93]. In patients with failed pancreatic grafts, perioperative management of glucose levels and acid-base status is the same as that for any diabetic patient.

4.6. Intestine transplant recipients

There are three types of intestine transplantation: isolated intestinal transplantation, transplantation of combined intestine, and liver graft or multivisceral transplantation. The biggest problem in intestinal transplantation is graft rejection, and it is the main reason for morbidity and mortality. The diagnosis of rejection is confirmed by clinical symptoms, endoscopic appearance, and pathological specimens taken by endoscopy [94].

Denervation and lymphatic dysfunction of the intestine affect intestinal permeability and absorption. If the intestinal mucosa barrier is damaged by ischemia, rejection, or enteritis, bacteria translocate into the bloodstream and infections are often observed [95]. Some of these patients develop diarrhea and lose weight in the early post-transplantation period. Any imbalance in the electrolyte and acid-base status should be timely corrected. Fluid administration should be closely monitored to assure sufficient splanchnic perfusion. Venous access is of major consideration for the anesthesiologist due to chronic use of total parenteral nutrition and its thrombotic complications [96].

5. Special cases

5.1. Trauma

It is generally assumed that immunosuppressed patients are more susceptible to the effects of soft tissue damage and poor bone healing. Bone loss associated with chronic immunosuppressive therapy is a serious problem for most transplant recipients. These patients are prone to fractures (i.e. hip or compressive vertebral fracture) [97].

Only a few studies of traumatized transplant recipients have been reported. This is likely because of the infrequent presentation of these patients to trauma centers. The most common causes of trauma are car accidents and falls. The latest study by Scalea *et al.* determined that outcomes for traumatic injury in patients with organ transplants are not worse than that for non-transplant patients, despite common presumptions among physicians [98]. Transplant recipients sustaining trauma should receive the same initial resuscitation as any trauma victim. Patients should be assessed by a transplant surgeon as soon as possible and graft function should be closely assessed by a transplant team during hospitalization and after discharge from the trauma center [3]. Acute organ rejection within 6 months of admission for trauma is reported among 17% of solid organ recipients [99].

Transplant recipients, whose immune systems are already suppressed to prevent organ rejection, are presumed to be at greater risk of infection from traumatic injury. However, this was not observed in two latest studies [100]. Therefore, similar protocols of antimicrobial therapy should apply to both transplanted and non-transplanted patients to avoid the overuse of antimicrobial agents and ensure maintenance of the susceptibility patterns of pathogens.

Studies also show that transplanted organs are rarely injured in traumatic events. This is most likely related to careful selection of transplant recipients who are committed to self-care and continue to pursue healthy life style after transplantation.

5.2. Pregnancy

With the advances in transplantation medicine, female organ transplant recipients are able to conceive and carry pregnancies successfully to term. This state presents a unique challenge to attending physician, obstetrician, and anesthesiologist. These women are at an increased risk of comorbidities and obstetric complications. Therefore, all post-transplant pregnancies should be considered as high risk, and close monitoring is mandatory. Anesthesiologists are involved in the care of these patients for both labor analgesia and operative procedure. Anesthetic considerations include the effects of the physiologic changes of pregnancy on the transplanted organ, graft function in the peripartum period, and the maternal side effects and drug interactions of immunosuppressive agents. Anesthetic management should consider the important task of protecting graft function [101, 102].

Data are lacking regarding the optimal transplant-conception interval. The 2005 American Society of Transplantation Consensus Conference suggested that pregnancy 1 year after transplant is safe as long as the patient has stable graft function. This means: no episodes of rejection in the past year, a low risk for opportunistic infections, stable renal function (including in those receiving organs other than a kidney), and a low stable dose of maintenance immunosuppression [103].

Pregnancy does not appear to cause excessive or irreversible problems with graft dysfunction if the function of the transplanted organ was stable prior to pregnancy [104]. Maternal side effects of immunosuppression therapy include nephrotoxicity, hepatotoxicity, diabetes, and arterial hypertension, which could lead to possible dangerous complications. In kidney, heart, or heart-lung transplant recipients, the rate of complications, such as pre-eclampsia, premature labor, and risk of acute allograft rejection postpartum, is higher than that in the non-transplant population [105].

Current immunosuppressant drugs are not thought to be teratogenic and their use cannot be discontinued during pregnancy. All immunosuppressants cross the placenta. They are not strongly associated with the increased risk of congenital anomalies in the first trimester. However, they affect the immune system of fetus during the second and third trimesters and may result in premature delivery and low birth weight in newborn [106].

The anesthetic technique for cesarean section depends on indication, functional status of transplanted organ, and cardiovascular and hematological status. Central neuraxial blocks are not contraindicated if coagulation status is normal. However, documentation of paresthesia is important if regional anesthesia is planned. In the case of general anesthesia, all intravenous anesthetics and inhalational agents are safe. Neuromuscular function should be monitored particularly if the patient is receiving magnesium. Postoperative pain relief is provided with narcotics by epidural or spinal route if regional anesthesia is used or by parenteral opioids. Non-steroidal anti-inflammatory drugs should be avoided. Thromboprophylaxis should be administered because of the high risk of thromboembolic complications in these patients, especially after cesarean delivery. The threshold for admission to an intensive care or high-dependency unit should be low [107].

5.3. Laparoscopic surgery

Laparoscopic surgery is currently a widely accepted approach to several surgical fields because of its advantages in terms of postoperative pain reduction and easy patient recovery. The number of minimally invasive surgical procedures performed in transplant recipients is constantly increasing [108].

Lymphoceles can be successfully treated surgically after kidney transplantation by laparoscopy under general anesthesia [109, 110]. There are also reports of successful laparoscopic bariatric surgery after simultaneous pancreas and kidney transplantation [111]. Laparoscopic cholecystectomy is considered to be safe procedure in the transplant population. It has advantage of short hospital stay, low morbidity, maintenance of oral immunosuppression, and early return to preoperative routines. There is however a slightly higher rate of conversion to an open cholecystectomy among transplant patients compared to general population (27% vs. 11%, respectively) [112, 113]. Generally, laparoscopic approach may be useful even in solid-organ transplantation surgery as a diagnostic or treatment procedure in some surgical complications.

5.4. Outpatient and esthetic surgery

With shorter medical procedure duration and fewer complications, there is growth in popularity of outpatient or ambulatory surgery. Procedures performed are broad in scope: knee, shoulder, spine and eye surgery (cataract, laser surgery), plastic surgery, some types of esthetic surgery, and upper gastrointestinal endoscopy and colonoscopy [114].

Improved immunosuppression and lifespans have afforded solid organ transplant recipients the opportunity to seek outpatient and esthetic surgery. Most commonly performed procedures are soft tissue excisions with local flap coverage, facelifts, breast augmentation, and abdominoplasty. Among solid organ transplant recipients, kidney transplant recipients most often underwent plastic surgery, accounting for over 68% [115]. The complication rate is very low and ranges from 4 to 8% [116]. Delayed wound healing or wound disruption is reported as the most common complication and is associated with immunosuppression therapy, such as steroids [117].

It is extraordinarily important to manage these patients with a multidisciplinary approach. They should obtain clearance from the transplant surgeon and from the organ-specific specialist. The anesthesiologist should be familiar with the organ-specific needs in the perioperative period (i.e. maintaining preload for heart transplant patients, judicious fluid management in the renal patient, and avoidance of volatile anesthetics in liver transplants) to avert unintended consequences. It is more reasonable to use of general anesthesia over regional in the heart transplant patients. Perioperative antibiotic prophylaxis and stress-dose steroids should be administered prior to surgery. NSAIDs should be avoided in postoperative pain regimen [118].

Elective esthetic surgery can be performed safely in patients with a history of solid organ transplantation after a careful patient selection and multidisciplinary approach. These patients can potentially experience significant improvements in their quality of life with low morbidity.

6. Conclusion

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. Local, regional, or general anesthesia can be safely delivered to transplant recipients and a successful anesthetic and perioperative management can be provided. However, for the safe management of solid organ recipients, it is essential to have an appropriate knowledge of the physiology of the transplanted organ, the pharmacology of the immunosuppressive drugs, and the presence of associated organ dysfunction.

Many of the perioperative problems in the transplant population have not been specifically studied, and there are no formal recommendations for their management. Additional research should be performed in order to identify perioperative issues and facilitate the formulation of guidelines for anesthesia in this particular transplanted population.

Conflict of interest

The authors declare no conflict of interest.

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