Anesthetic Management of Adult Transplant Recipients for Non-transplant Surgery

Essay

Submitted for partial fulfillment of master degree in anesthesiology

By

Sameer Mustafa Muhammad Abdelbasit

(MB, B,CH)

Supervised by

Prof.Dr/ Fekri Fouad Ahmad El-bokl

Professor of Anesthesiology and Intensive Care Medicine

Faculty of Medicine- Ain Shams University

Dr. / Azza Atef Abdelalim

Assistant professor of Anesthesiology and Intensive Care Medicine

Faculty of Medicine- Ain Shams University

Dr. / Ashraf El-Sayed El-Agamy

Lecturer of Anesthesiology and Intensive Care Medicine

Faculty of Medicine- Ain Shams University

Faculty of Medicine

Ain Shams University

2009

Acknowledgments

First of all, I thank and praise **ALLAH**

I would like to express my deepest gratitude and sincere thanks to my principal supervisor **Prof. Dr. Fekri Fouad Ahmad El-bokl, professor of anesthesia and intensive care, faculty of medicine, Ain Shams University**. For his continuous encouragement and constructive guidance in the initiation and progress of this work.

I would like to express my deepest thanks and appreciation to **Dr. Azza Atef Abdelalim, assistant professor of anesthesia and intensive care, faculty of medicine, Ain Shams university**. For her great support, helpful suggestions and sincere effort.

I also fell obliged to **Dr. Ashraf El-Sayed El-Agamy, lecturer of anesthesia, faculty of medicine, Ain Shams University**. Who helped and guided me in this work to very last detail.

Finally to **my family** that provided the good atmosphere for me to continue the work, beside their great psychological and moral support.

Sameer Mustafa Muhammad Abdelbasit.
Cairo, 2010

Table of Contents

List of Tables

List of Abbreviations

AV	**Atrioventricular**
AZA	**Azathioprine**
BO	**Bronchiolitis Obliterans**
CMV	**Cytomegalovirus**
CSA	**Cyclosporine**
EBV	**Epstein-Barr virus**
ECG	**Electrocardiogram**
ESRD	**End-stage renal disease**
FEF	**Forced expiratory flow**
FEV	**Forced expiratory volume**
FEV1	**Forced expiratory volume in the first second**
FVC	**Forced Vital Capacity**
GFR	**Glomerular filtration rate**
HIV	**Human Immune Deficiency Virus**
HPS	**Hepatopulmonary syndrome**
IL	**Interleukin**
IMP	**Inosine monophosphate**
INR	**International normalized ratio**
LDL	**Low Density Lipoprotein**
VLDL	**Very Low Density Lipoprotein**
MAC	**Minimum alveolar concentration**
MAO	**Monoamine Oxidase**
MMF	**Mycophenolate mofetil**
NAPRTCS	**North American Pediatric Renal Transplant Cooperative Study**
NSAIDS	**Non Steroidal Anti- inflammatory Drugs**
NYHA	**New York Heart Association**
OHT	**Orthotopic heart transplantation**
OLT	**Orthotopic liver transplantation**
PEEP	**Positive end expiratory pressure**
PPH	**Porto- pulmonary hypertension**
SLT	**Single lung transplantation**
TIVA	**Total intravenous anesthesia**
TLC	**Total Lung Capacity**
TPN	**Total parenteral nutrition**

Introduction

The number of organ transplantations is increasing and the survival of the transplanted organs and patients is continually improving ***(Toivonen, 2000)***.

Transplant recipients have considerable medical, physiological and pharmacological problems of allograft denervation, the side effects of immunosuppression, the risk of infection, and the potential for rejection ***(Brone et al.,1997)***.

Therefore, a clear understanding of the physiology of the transplanted organ, the pharmacology of the immunosuppressive drugs and the underlying surgical conditions is essential for these patients to safely undergo anesthesia and surgery ***(Kostopanagiotou et al., 1999)***.

The transplanted recepients are frequently exposed to elective or emergency nontransplant surgery either related to the transplant procedure, like biopsies, draining, infections, and endoscopies or unrelated like polytrauma or delivery.

There are specific anesthetic considerations with each graft transplant. The individual case is to be dealt with on a case-by-case basis and it remains the responsibility of the anesthetist to work hand in hand with the surgeon and the post-surgical ICU specialist to coordinate their assessment to reach the best possible management ***(Hariharan, 2001)***.

Aim of the work

The aim of this work is to define the guidelines of anesthetic management for transplant recipients in non-transplant surgery and to determine the possible complications in such cases in order to safeguard the surgical and anesthetic outcome with minimal hazards.

Pharmacological Considerations and Drug Interactions

The major advance allowing prolonged graft survival has been the use of immunosuppressive drugs that downregulate the immune response. The immunosuppression that is used varies among centers and evolves with the development of new medications. The standard triple therapy of prednisone, azathioprine (AZA), and cyclosporine A (CSA) that was used in most patients (80% - 85%) from 1987 to 1993 decreased in use to only 30% in 1996. This decrease is attributed to the introduction of mycophenolate mofetil (MMF) to replace AZA. The use of MMF increased from 6.5% to 35.8% from 1996 to 1997. During this time period, the use of CSA and prednisone remained stable: 83.1% versus 79.6% and 96.2% versus 95.4%, respectively. The use of AZA decreased from 50% to 35.8%, and the use of tacrolimus increased from 2.5% to 10.8%. ***(Hariharan, 2001)***. Recently, the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) 2001 Annual Report demonstrated continued changes in immunosuppressive strategies. Among patients who underwent transplants in 2000, 59.8% received CSA, 36.2% received tacrolimus, 74.4% received MMF, and 11.6% received AZA at day 30 after transplant.

INDUCTION AGENTS

The goal of induction therapy is to prevent T-cell activation. This goal can be achieved either through depleting the T-cell pool with monoclonal or polyclonal antibodies or by specifically inhibiting the action of the cytokine, interleukin-2 (IL-2). The choice of induction therapy depends on the center and patient **(Table 1)**. The two main issues to consider in choosing the appropriate agent are its efficacy in that patient population and its side-effect profile ***(Mark T. Keegan, 2004)***.

Table 1: Current immunosuppressive drugs and approaches for intestinal or multivisceral transplantation.

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

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

OKT3

Muronab-CD3 (Orthoclone, OKT3) is a monoclonal antibody that binds to the lymphocyte-CD3 complex. OKT3 has been used as an induction therapy. OKT3 is effective at reversing acute rejection, but often subsequent treatments are limited because of the production of anti-OKT3 antibodies ***(Mayes et al., 1988)***. Side effects of antilymphocyte therapy

can be divided into two separate categories: (1) infusion-related side effects related to a foreign protein being administered and (2) drug-related side effects related to activated T-cell depletion. Infusion-related side effects include fever, chills, hypotension, nausea, diarrhea, and potentially life-threatening anaphylaxis.

Antilymphocyte Globulin and Antithymocyte Globulin

Antithymocyte globulin (equine) (Atgam) is a polyclonal horse-derived antilymphocyte globulin. A newer agent, antithymocyte globulin (Thymoglobulin), is a rabbit-derived antithymocyte globulin. Although prolonged lymphocyte suppression was observed in the Thymoglobulin group, there was no increase in infection or malignancy at 1 year after induction ***(Brennan et al., 1999)***.

Antibodies to interleukin-2 receptor

Basiliximab

Basiliximab (Simulect) is a chimeric human/mouse monoclonal antibody that is directed to the alpha chain of the IL-2 receptor on the surface of activated T cells.

Overall, Basiliximab is well tolerated and has a side-effect profile that is similar to placebo ***(Kahan et al., 1999)***. Basiliximab does come with one strong warning. Severe acute hypersensitivity reactions have been observed in patients with the initial and reexposure dose. This acute reaction may include hypotension, tachycardia, cardiac failure, dyspnea, bronchospasm, pulmonary edema, respiratory failure, urticaria, rash, or sneezing. Appropriate medications should be available in the event of such a reaction.

Daclizumab

Daclizumab (Zenapax) is a humanized monoclonal antibody to the alpha chain of the IL-2 receptor.

Administration of Daclizumab in addition to dual (CSA and corticosteroids) ***(Nashan et al., 1999)*** and triple (CSA, corticosteroids, AZA) ***(Vincenti et al., 1998)*** immunosuppressive therapy was found to reduce significantly the rate of acute allograft rejection. No specific adverse reaction to Daclizumab was noted in either study group ***(Vincenti et al., 1998)***.

MAINTENANCE IMMUNOSUPPRESSION

Steroids

Steroids have broad anti-inflammatory effects on cell-mediated immunity but leave humoral immunity relatively intact ***(Krensky et al., 1994)***. Steroids have multiple adverse effects, however, including cushingoid habitus, susceptibility to infection, impaired wound healing, growth suppression in children, osteoporosis, aseptic necrosis of bone, cataracts, glucose intolerance, fluid retention, hypertension, emotional liability, insomnia, manic and depressive psychosis, gastric ulcer disease, hyperlipidemia, polyphagia, obesity, and acne. The use of steroids in pediatrics is currently standard practice, but the side effects and complications associated with long-term steroid use are greatest in this population.

Calcineurin inhibitors

Cyclosporine

Cyclosporine A (Sandimmuine) is a cyclic peptide of fungal origin that inhibits T-cell response. It binds to cellular proteins called cyclophilins, and this complex inhibits the movement of transcription factors into the nucleus, blocking IL-2 production. This cascade of events ultimately results in inhibition of T-cell proliferation and differentiation ***(Sarwal et al., 2001)***. The side effects of CSA include hepatotoxicity, hypertension, hyperkalemia, hirsutism, gingival hyperplasia,

susceptibility to infection, and increased risk of malignancy. CSA has many drug interactions, especially with drugs that are metabolized by the cytochrome P-450 system of the liver. The use of the new microemulsion form of CSA (Neoral) has significantly increased since its introduction. The monitoring of CSA levels early in the post transplant period is critical. A generic form of CSA, SangCyA, recently has become available.

Sirolimus was first studied and approved by the Food and Drug Administration in combination with CSA after renal transplantation ***(Wyeth Laboratories, 2001)***. Because of the synergistic immunosuppressive effect of the Sirolimus-CSA combination, CSA dosage and target levels are lower ***(Khanna, 2000)***.

Tacrolimus

Tacrolimus (Prograf, FK506) is a product of the fungus Streptomyces tsukubaenis, and although it is a macrolide like cyclosporine, it differs in its chemical structure and cytosolic binding site. Tacrolimus interacts with the FK binding protein and inhibits T-cell derived lymphokines, including IL-2, IL-3, and IL-4, gamma interferon, and inhibiting the clonal expansion of helper and cytotoxic T cells ***(Schenck et al., 1991)***.

There was an increased incidence of lymphoproliferative disease in the tacrolimus treatment group, which may limit its use, especially in the Epstein Barr virus-negative patient who receives an Epstein Barr virus-positive allograft. Other major side effects of tacrolimus are similar to CSA and include neurotoxicity, diabetes and infection. The use of tacrolimus as primary immunosuppression has increased and recently, several centers have reported the use of tacrolimus as a rescue agent in the setting of acute and chronic rejection ***(Shapiro, 1998)***.

Antiproliferative Agents

Azathioprine

Azathioprine (Imuran), a prodrug of the chemo-therapeutic agent 6- mercaptopurine, acts by directly inhibiting the growth and differentiation of immune cells. After metabolism in the liver, derivatives of the prodrug inhibit purine synthesis, which prevents gene replication and cell division ***(Benfield et al., 1999)***. In addition to blocking cell-mediated immunity, it inhibits primary antibody synthesis and decreases circulating monocytes and granulocytes ***(Krensky et al., 1994)***. The major side effect of AZA is myelosuppression with leukopenia, thrombocytopenia, and megaloblastic anemia. Other side effects include susceptibility to viral infection, hepatotoxicity, pancreatitis, alopecia, and neoplasia.

Mycophenolate mofetil

Mycophenolate mofetil (Cell-Cept) recently gained acceptance as a first-line agent as a replacement for AZA as part of the standard triple therapy. It is an antimetabolite agent that interrupts purine metabolism in B and T lymphocytes. In vivo, it is rapidly metabolized to rnycophenolic acid, which blocks conversion of inosine monophosphate (IMP) to guanosine IMP in the purine biosynthetic pathway. The net result is a decrease in the number of functional B and T lymphocytes and inhibition of the response of human lymphocytes to antigen challenge ***(Young et al., 1994)***.

MMF is well tolerated, with hematologic and gastric side effects being the main concerns. Practitioners should follow blood counts looking for neutropenia and thrombocytopenia. If hematologic problems are noted, decreasing or holding the dose is recommended until values normalize. Gastric side effects include diarrhea, nausea, dyspepsia, and vomiting. If the patient has difficulty tolerating

MMF, the dose can be split into three to four smaller doses throughout the day. Switching the patient to the liquid form also can help with gastric complaints. Frank esophagitis and gastritis with occasional gastrointestinal hemorrhage occur in approximately 5% of patients ***(Gaston, 2001)***. MMF does not have any nephrotoxicity but should not be used in combination with AZA for fear of increased risked of neutropenia and infection. MMF is not metabolized by any of the cytochrome P-450 isoenzymes.

Sirolimus

Sirolimus (Rapamune, rapamycin) is a new immunosuppressive agent recently approved by the Food and Drug Administration for use in solid organ transplantation. It is a natural fermentation product of Streptomyces hygroscopicus and forms a complex with FK binding proteins in lymphocytes that interacts with a target protein that has yet to be fully characterized ***(Dumont et al., 1992)***. It has a unique mechanism of action that seems to block cytokine-mediated proliferation of T and B cells by interrupting second messenger signaling.

In phase I and phase II trials in adults, sirolimus was well tolerates and exhibited no apparent nephrotoxic properties or deleterious effects on blood pressure. Several groups have reported a significantly higher incidence of myelosuppression and hyperlipidemia ***(Sirolimus European Renal Transplant Study Group, 1999)*** with sirolimus therapy, but these side effects usually improve with dose reduction. The drug interaction with CSA and sirolimus is an important one. It is greatly related to administering both drugs at the same time.

Table 2: Some of the more common side effects associated with some immunosuppressive drugs that have a direct impact on anesthetic and perioperative management.

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

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

***** Fever, chills, hypotension, bronchospasm.

! Only when given intravenously.

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