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EDITOR'S NOTE

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Heart Transplant Surgeon, MS, MCh. (AIIMS, New Delhi), FACC.
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Greetings dear Colleagues,

In this edition of The Revival, Dr Manoj Kumar Sahu, Additional Professor Intensive Care Department of CVTS at AIIMS, New Delhi, walks us through the peri operative management of heart transplantation. Dr Sahu has covered this complex pathway in a very lucid and precise manner as per the AIIMS protocol. I understand each of the busy transplant institutes in India, will have their own set of standard operating protocols, but I feel this article will be a guide for centres wanting to start a transplant programme and are looking at experienced centres for protocols.

Editor's tips: The Donor and Recipient HLA cross match is crucial to prevent Primary Graft Dysfunction. In my unit it is mandatory to await the reports before recipient induction. This prevents on table primary graft dysfunction catastrophes. Also, a repeat PRA test is a must for a patient, who has been waiting for long on the list. All the preoperative patients are instructed to inform the unit in case there are any small incidents even if it sounds trivial (For e.g., there have been incidents where patients staying in a rural area had platelet transfusions by local physicians for dengue fever induced thrombocytopenia making them more at risk for graft rejection). Once the patient is wait listed all major or minor ailments should be attended to by the transplant unit. Anticoagulant drug list should be flagged in all recipients. Warfarin/Acenocoumarol are the drugs of choice to have on board for intra cardiac clots, because it's easier to reverse. Tab Amiodarone should be removed from the list of pre-operative medications, in view of higher incidence of PGD related to amiodarone use. Covid vaccination is also a must for pre-operative and post-operative patients.

I thank Dr Sahu for his contribution as a Guest author for the May 2021 issue of The Revival.

- Dr. Manoj Durairaj
Editor "The Revival"

SUB EDITOR

Dr. Talha Meeran
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Dear Colleagues,

This edition of The Revival features Dr Sahu, from AIIMS, Delhi as our guest author. He lays down a concise yet descriptive and easy to read summary on the perioperative management of cardiac transplant patients. Of note, is the complications section where Dr Sahu has provided an exhaustive list of all the possible complications that one can encounter post cardiac transplant including his quick summary on each of their management principles.
The editorial team appreciates Dr Sahu's academic contribution amidst this challenging phase of the ravaging COVID19 pandemic throughout our nation.

Sincerely,
Dr. Talha Meeran
Sub Editor "The Revival"

PRESIDENTIAL MESSAGE

Prof. (Dr) V. Nandakumar
Director & Chief, Division of Cardio Vascular/ Thoracic Surgery & Cardiac Transplantation, Metromed International Cardiac Centre, Calicut, Kerala.

Greetings from the Society for Heart Failure and Transplantation.

The May issue of The Revival comes with Dr. Manoj Kumar Sahu's article on "Perioperative management of Heart Transplant Patients" wherein he describes the entire process in a simple manner without compromising the significance of any aspect. This will be a helpful guide for any unit setting up a heart transplantation programme.

The second wave of the Covid-19 pandemic is affecting a larger population and with increased severity. We are ramping up for a mega vaccination drive. At this juncture, it is heartening to know that the Government is prioritizing the vaccination for heart failure, potential transplant and post-transplant patients. ISHLT Covid-19 task force has advised not to alter the patients' immunosuppression regimen after vaccination. "Since vaccination is safe and gives some level of immune protection, thoracic organ transplant recipients should be vaccinated" *(Source: ISHLT)*.

Let us hope that with extensive vaccination, this global pandemic will be under control and life as we knew it will resume in the near future!

- Prof. (Dr) V. Nandakumar
President

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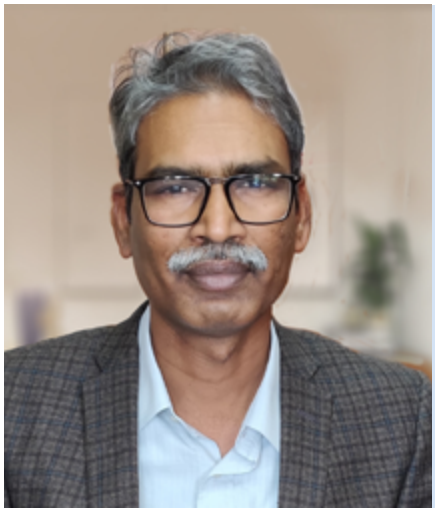
Special thanks to
Dr. Manoj Kumar Sahu for authoring this month's article.

Designed by Maithili Kulkarni

PERIOPERATIVE MANAGEMENT OF HEART TRANSPLANT PATIENTS



Dr. Manoj Kumar Sahu

Dr. Manoj Kumar Sahu is working as an Additional Professor in the Intensive Care for CTVS in all India Institute of Medical Science (AIIMS), New Delhi. He has completed his MD and DNB in Anaesthesiology & Critical Care from Banaras Hindu University, Varanasi and Diplomate National Board of Examinations, New Delhi respectively. He has been a part of the heart transplantation program of the Institute since 2012.

His interest areas are Thoracic organ transplantations, Extracorporeal membrane oxygenation and Pediatric Cardiac Intensive care.

Introduction

Heart transplantation (HTx) is accepted worldwide as a Gold Standard treatment option for End Stage Heart Disease. Heart Transplantation provides a substantial improvement in survival and quality of life. However, transplantation is not without risk, and transplant recipients will suffer some form of complication, which can range from mild to potentially fatal. Bleeding, kidney failure, primary graft dysfunction, allograft rejection, infection and immunosuppressant management remain the challenges in the early post-operative period.

Preoperative Evaluation of the Recipient:

Rule out active psychiatric diseases and assess family support

CT/MRI of the brain, chest, abdomen and carotid doppler are done to rule out pathologies in brain, lungs, liver and kidney.

A complete cardiovascular testing is performed with electrocardiogram, echocardiogram, coronary angiogram and right heart catheterization to measure the pulmonary artery pressure and document reversible pulmonary vascular disease prior to transplant.

Screening for endocrine diseases like diabetes, thyroid dysfunction and hematological disorders is done.

The recipient should be immunized against Influenza, Hepatitis & Pneumococcus

A complete list of laboratory investigations include the following -

- Blood grouping (ABO), Panel Reactive Antibody (PRA)
- Complete blood count, thyroid function tests, glycosylated hemoglobin (HbA1c)
- Biochemistry- renal & liver function tests, Lipids, Electrolytes, amylase, lipase etc.
- Coagulation parameters – Prothrombin time, International normalisation ratio and activated partial thromboplast in time
- Cardiac and inflammatory/infective biomarkers - CPK(MB), BNP, Trop-I, procalcitonin (PCT)
- Serology-Titers for HIV, Hepatitis, Cytomegalovirus (CMV), Ebstein-Barr virus (EBV), Varicella zoster virus(VZV), Toxoplasma, Rubella, HSV.
- Microbiological cultures (bacteria / viral / fungi / tuberculosis)
- Skin swab for methicillin resistant staphylococcus aureus (MRSA)

Preoperative orders before surgery:

Informed Consent, Part preparation & nil by mouth for 8 hours

Arrange Leukocyte depleted, irradiated CMV negative cross matched blood & products

Vitamin K 10 mg intramuscular injection

Antibiotic Prophylaxis (as per protocol)

Immunosuppressants - Tacrolimus 1 mg & Mycophenolate mofetil 500 mg per oral stat dose

Tab. Eltroxin 25 mcg oral stat dose

Tab. Sildenafil 25mg oral stat dose in selected patients

Intraoperative Management-

Arrival of donor heart in the operating room and starting recipient surgery is coordinated well, Surgery is performed under cardiopulmonary bypass (CPB), mild hypothermia at 32^0C. Methylprednisolone 500 mg IV is given at the time of aortic cross clamp (ACC) removal. Appropriate inotropes/ vasodilators are initiated while weaning from CPB, in some instances mechanical support like Intra aortic balloon erpulsation (IABP)/ Extra corporeal membrane oxygenation (ECMO) may be required. Chest is closed after thorough hemostasis and placing four epicardial pacing wires

Postoperative Management of HTx Recipient in the ICU

All HTx patients are received in intensive care unit (ICU)- sedated, intubated & ventilated.

These patients are nursed in single or double-bed rooms preferably with reverse isolation.

Strict asepsis is mandatory. Medical staff must disinfect their hands & put on gloves before performing any procedure. Visitors must be restricted.

Arrival in ICU- establish the hemodynamic monitoring & re-establish the mechanical ventilation.

Arterial blood gas is done to check oxygenation & ventilation, Activated clotting time is tested and residual heparin effect may be neutralized with protamine.

The aim is to achieve adequate cardiac output (CO). Optimize preload, afterload with appropriate fluids, inotropes and vasodilators. Ensure adequate organ perfusion and recovery.

The goal is to rehabilitate the patient to normal life – Early extubation, physiotherapy, mobilization, enteral nutrition and psychosocial assistance are the expected norms. Most patients are maintained on inotropic and chronotropic support for 36-72 hours. Extubation is typically achieved when hemodynamics are stable and bleeding is no longer a risk. Invasive monitoring and mediastinal drains are removed after mobilizing the patient, day 3 onwards. A patient who has an uncomplicated course may get discharged from the ICU within 72 hours, but most of them stay in ICU for 5 days on average.

Immunosuppressant (IS) therapy– Most transplant centers use triple drug regimen (tacrolimus, mycophenolate mofetil (MMF) and prednisolone as maintenance IS therapy. Tacrolimus 1mg & MMF 10mg/kg are started orally preoperatively few hours before surgery.

Methylprednisolone is started intraoperatively at 500mg/iv /at the time of ACC release and then continued postoperatively at same dose/iv/ 8 hourly (2 more doses) - followed by - 1mg/kg/day iv in 2 divided doses, till the target tacrolimus blood level is achieved. Then methylprednisolone is converted to oral prednisolone which is tapered gradually and kept going at a dose of 5mg per day

Tacrolimus and MMF are again re-started from postoperative day 2 onwards keeping close watch on renal function. We monitor the blood Tacrolimus levels twice a week and aim at the target trough levels-1st 2 months =10–15 ng/ml, 2–6 months = 8–12 ng/ml, and after 6 months = 5–10 ng/ml). **MMF is continued** at - 500 - 1500 mg twice daily (check with WBC counts, target 5000–7000/µl)

Induction agents (IA) – are required in certain special situations/cases like marginal donor hearts/preoperative renal impairment/or if some center has been using IA as a protocol. IL-2 Receptor Antagonists (Basiliximab) - 12 mg/m2 up to 20 mg per dose over 30 min on day 0 and day 4.

Other Postoperative medications include– Antibiotics, analgesics as per protocol. Pulmonary vasodilators like (Sildenafil) are started from day 0 if indicated for pulmonary artery hypertension. Other important medications like Valganciclovir (antiviral drug) for CMV prophylaxis, trimethoprim-sulfamethoxazole for Pneumocystis carinii and Voriconazole for antifungal prophylaxis are mandatory - started from day 2 onwards, once the patient is stabilized with good hemodynamics and normal kidney function.

Early Postoperative problems and management-

a) **Bleeding–** Watch closely for cardiac tamponade

b) **Sinus node dysfunction–** Maintain target heart rate of 100/min, normal sinus rhythm & intact A-V conduction is helpful in achieving good CO.

c) **Ventricular dysfunction–** treated using inodilators (dobutamine/ milrinone).

d) **Increased pulmonary vascular resistance (PVR)–** managed with inhaled nitric oxide(iNO), sildenafil and avoiding hypercapnia, hypoxia, acidosis and hypothermia.

e) **Vasoplegia and severe hypotension– Maintain** optimal preload (CVP of 10-12 mmHg) and MAP > 70 mmHg. vasoactive and inotropic agents are adapted accordingly.

f) **Hypertension– may** be due to larger heart size (big heart syndrome), baroreceptor dysregulation and drug (calcineurin inhibitors) effects and it is controlled with iv vasodilators(NTG/SNP) initially and then by calcium channel blockers

g) **Primary graft failure (PGD)–** manifests as heart failure

without any anatomic or immunologic etiology. IABP/ VA ECMO are initiated early to support the failing heart if doesn't respond to pharmacotherapy.

h) **Renal dysfunction–** These patients need appropriate fluid management, optimal filling pressure and diuretics If the recipient becomes anuric/oliguric/ serum creatinine rises sharply- hemodialysis is instituted and initiation of tacrolimus is delayed.

i) H**yperacute Rejection–** occurs within 1st 24 hours, intraoperatively and manifests as failure to wean off CPB

Intraoperative endomyocardial biopsy (EMB) is done to confirm the diagnosis.

The condition is treated with high dose corticosteroid (CS), Plasmapheresis, iv IgG

Cytolytic therapy- Rituximab, IV Cyclosporin / Tacrolimus and MMF (if no response to No-2)

Inotropes and vasopressors to stabilize the hemodynamics and implementation of mechanical circulatory support devices (MCSD) if hemodynamics deteriorates despite maximal pharmacotherapy

j) **Acute Cellular Rejection (ACR)–**

An endomyocardial biopsy (EMB) should be performed as early as possible

Pulse steroid therapy (high dose methylpresdnisolone) is given as first-line therapy for symptomatic ACR irrespective of ISHLT EMB grade (1R, 2R or 3R).

Cytolytic IS therapy with Polyclonal Antibody - anti-thymocyte antibodies (ATGAM)/ Monoclonal Antibody (OKT3) – are administered in addition to steroids if hemodynamic compromise is present and especially if there is no clinical improvement within 12 to 24 hours of pulse therapy

Inotropes, vasopressors and MCSD are required to maintain adequate CO until recovery of heart allograft function occurs

k) **Antibody Mediated Rejection (AMR)–** is the antibody-mediated response to mismatched HLAs (existing antibody to donor specific antigens on graft endothelium). AMR results in graft ischemia, thrombosis and cell death in minutes to hours and is uniformly fatal.

Ventricular dysfunction without significant ACR on EMB is an indirect indication of AMR

Treatment- Pulse steroids, Iv IG, Plasmapheresis and Rituximab (anti B-cell CD-20)

CONCLUSION:

1. Heart Transplantation still remains the gold standard for ESHF patients
2. A thorough pre-operative evaluation of recipients is done to rule out the contraindications for HTx, they are immunized before, their PRA, blood group and weight etc. are recorded.
3. Storage and Transport of hearts from distant places (outstation hearts) need to be addressed diligently, Ischemia time exceeding 4 hours is a big risk for allograft rejection/PGD postoperatively.
4. Early postoperative period is heralded by many complications starting from bleeding, tamponade, arrhythmias, to dangerous ones like PGD and acute allograft Rejection
5. The transplant centre should have adequate back-up to manage PGD or Rejection with antirejection drugs and the circulatory assist devices like ECMO/VAD etc.
6. Infection is a major challenge, which needs to be diagnosed and treated timely
7. Renal failure is a major risk in the early postoperative period, can be averted with judicious management of fluid and IS therapy.
8. Hyperacute rejection occur intraoperatively soon after weaning CPB, or may fail to wean off CPB - diagnosed with EMB and treated immediately while supporting the heart pharmacologically and mechanically.
9. **Acute rejection episodes are to be diagnosed & treated early and efficiently with pulse steroid therapy, upregulation of immunosuppressants and other measures (e.g., plasmapheresis, iv IG, IAs etc.).**

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